Κολπική μαρμαρυγή και στεφανιαία νόσος: Νέα δεδομένα, νέες στρατηγικές για συνδυασμένη αντιπηκτική - αντιαιμοπεταλιακή αγωγή

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Ιατρικής Σχολής Πανεπιστημίου Αθηνών,

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Epidemiology and AF and PCI

AF and CAD often occur together because of the strong association of both conditions with aging and overlapping risk factors.

@ 1 Billion people in US and Europe
@ 20 Million with AF (1-2% of population)\(^1,2\)
@ 16 Million anticoagulation indicated (80%) \(^1,2\)
@ 4.8 Million have CAD as well (20%-45%) \(^1,2\)
@ 1-2 Million potential revasc (20%-25%) \(^3,4\)

1. The AFFIRM Investigators. *Am Heart J* 2002;143:991–1001;
Incidence of Atrial Fibrillation in ACS Patients

2 % to 21% of ACS Patients

Quiz:

When Does 1 + 1 = 5?
ACS + Afib = 5 X the in hosp. mortality of ACS alone
Persistent Elevation of Thrombin Generation in Post-ACS Patients

Merlini et al. Circ 1994;90:61-68
Positive Feedback Loop: Thrombin Begets Platelet Activation Which Begets Thrombin

Slide by C. Michael Gibson, M.S., M.D., D.D.
The Optimal Management of Atrial Fibrillation and ACS Differ

Atrial Fibrillation (ACTIVE W) 1: The combination of aspirin and clopidogrel is not as effective as warfarin in patients with AF.

However

Stenting (STARS) 2: The combination of aspirin and clopidogrel is more effective than warfarin in patients with coronary stents.
## Bleeding Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel + ASA* n=6,259</th>
<th>Placebo + ASA* n=6,303</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding†</td>
<td>3.7%</td>
<td>2.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2%</td>
<td>1.8%</td>
<td>0.13</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.6%</td>
<td>1.0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5.1%</td>
<td>2.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Bleeding Associated with Warfarin, Aspirin, Clopidogrel in Patients with AF n=82,854

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin monotherapy</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td>0.93 [0.88-0.98]</td>
</tr>
<tr>
<td>Clopidogrel monotherapy</td>
<td>1.06 [0.87-1.29]</td>
</tr>
<tr>
<td>Aspirin + clopidogrel</td>
<td>1.66 [1.34-2.04]</td>
</tr>
<tr>
<td>Warfarin + aspirin</td>
<td>1.83 [1.72-1.96]</td>
</tr>
<tr>
<td>Warfarin + clopidogrel</td>
<td>3.08 [2.32-3.91]</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>3.70 [2.89-4.76]</td>
</tr>
</tbody>
</table>
Heparin activates platelets

Control platelets

Platelets treated with UFH

% of platelets binding PAC-1*

% of platelets expressing p-selectin (activated platelets)

UFH 1.2 U/mL (PCI level)
UFH 2 U/mL (High dose)
UFH + Eptifibatide (PCI levels)
Bivalirudin (PCI dose level)

Thrombin conc (U/mL)

Am J Cardiol 2007; 100:417. Cor Ar Dis 2006; 17:471
## Limitations of Vitamin K Antagonists (Warfarin)

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset and offset of action</td>
<td>Overlap with parenteral agent</td>
</tr>
<tr>
<td></td>
<td>Need for reversal agent or prolonged time to procedures</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Narrow therapeutic window</td>
<td>Increased monitoring</td>
</tr>
<tr>
<td></td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td></td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td></td>
<td>Multiple food and drug interactions</td>
</tr>
</tbody>
</table>

Bates SM et al *Br J Haematol* 2006;134: 3-19
Factor Xa Inhibition: At The Intersection of the Intrinsic and Extrinsic Pathways

If either the Intrinsic or Extrinsic pathway is activated, Factor Xa inhibitors block the final common coagulation pathway to form thrombin by blocking Factor XA.
Effects of Rivaroxaban, ASA and Clopidogrel Alone and in Combination in a Porcine Model of Stent Thrombosis

- Dual antiplatelet therapy with ASA + clopidogrel decreased thrombus mass by 79%
- The combination of ASA and rivaroxaban significantly inhibited thrombus mass by 86%
- Addition of the anticoagulant rivaroxaban to ASA + clopidogrel produced further improvement
- Rivaroxaban + clopidogrel + ASA inhibited stent thrombus by 98% (P<0.001)

Rivaroxaban dose: 1 μg/kg/min.
Error bars are the standard error of the mean.
***P<0.001 (unpaired t-test vs representative vehicle group).
EFFICACY ENDPOINTS:
Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine

Estimated Cumulative Incidence (%)

CV Death / MI / Stroke
Placebo
- HR 0.85
- mITT
- p=0.039
- ITT
- p=0.011
Rivaroxaban
- 2.5 mg BID
- NNT = 71

Cardiovascular Death
Placebo
- HR 0.62
- mITT
- p<0.001
- ITT
- p<0.001
Rivaroxaban
- 2.5 mg BID
- NNT = 59

All Cause Death
Placebo
- HR 0.64
- mITT
- p<0.001
- ITT
- p<0.001
Rivaroxaban
- 2.5 mg BID
- NNT = 56

Slide by C. Michael Gibson, M.S., M.D.
STENT THROMBOSIS
ARC Definite / Probable / Possible

**Estimated Cumulative Incidence (%)**

- **Placebo**: 2.9%
- **Rivaroxaban** (both doses): 2.3%

**HR** 0.69
(0.51 - 0.93)

**mITT** p = 0.016

**ITT** p = 0.008

ARC Definite/probable: HR=0.65, mITT p=0.017, ITT p=0.012

2 Yr KM Estimate
### ATLAS ACS 2-TIMI 51: Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban 2.5 mg BID n = 5114</th>
<th>Rivaroxaban 5 mg BID n = 5115</th>
<th>Placebo n = 5113</th>
<th>HR (95% CI) 2.5 mg</th>
<th>HR (95% CI) 5 mg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>9.1%</td>
<td>8.8%</td>
<td>10.7%</td>
<td>0.84 (0.72-0.97)</td>
<td>0.85 (0.73-0.98)</td>
<td>.02</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>2.7%</td>
<td>4.0%</td>
<td>4.1%</td>
<td>0.66 (0.51-0.86)</td>
<td>0.94 (0.75-1.20)</td>
<td>.002</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>1.8%</td>
<td>2.4%</td>
<td>0.6%</td>
<td>3.46 (2.08-5.77)</td>
<td>4.47 (2.71-7.36)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>0.67 (0.24-1.89)</td>
<td>1.72 (0.75-3.92)</td>
<td>.45</td>
</tr>
</tbody>
</table>

*Mega JL, et al. [5]*
Treating AF with Concomitant ACS Is a Balancing Act

Thromboembolic risk
Patients with ACS and AF are at risk of both a second myocardial infarction\(^1\) and a stroke\(^2\)

Bleeding risk
Risk of bleeding increases with the number of antithrombotic agents\(^3\)

---

WOEST Primary Endpoint: Bleeding

Events TIMI Classification

<table>
<thead>
<tr>
<th>TIMI Classification</th>
<th>Double therapy group</th>
<th>Triple therapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>6.5</td>
<td>16.7</td>
</tr>
<tr>
<td>Minor</td>
<td>11.2</td>
<td>27.2</td>
</tr>
<tr>
<td>Major</td>
<td>3.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Any TIMI bleeding</td>
<td>19.5</td>
<td>44.9</td>
</tr>
</tbody>
</table>

$p<0.001$ for all comparisons
WOEST All-Cause Mortality

Cumulative incidence of death

- Triple therapy group
- Double therapy group

HR = 0.39, 95% CI [0.16-0.93]

\( p = 0.027 \)

n at risk:
- Triple therapy: 284, 281, 280, 280, 279, 277, 270, 252
- Double therapy: 279, 278, 276, 276, 276, 275, 274, 256
**AF patient in need of OAC after an ACS**

- **Bleeding risk low** compared to risk for ACS or stent thrombosis
- **Bleeding risk high** compared to risk for ACS or stent thrombosis

**Time from ACS**
- 0
- 1 month
- 3 months
- 6 months
- 12 months
- Lifelong

**OAC monotherapy**
- **OAC**
- Aspirin 75–100 mg daily
- Clopidogrel 75 mg daily

**Triple therapy** (IIaB)
- **Triple therapy** (IIaB)

**Dual therapy** (IIaC)
- **Dual therapy** (IIaC)

**Figure 12** Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

*Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.*

*OAC plus single antiplatelet.

*Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.*
Figure 13  Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation.
A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110mg b.i.d. and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor with aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI).

**STUDY TITLE**

D110 plus a P2Y12 inhibitor is:
Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)
AND
Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

**STUDY HYPOTHESES**

D150 plus a P2Y12 inhibitor is:
Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)
AND
Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

**Worldwide Event Driven Trial**

Paroxysmal, persistent or permanent AF (PCI with stenting [BMS or DES] elective or ACS)

- **Screening**
- 0-72 hours post-PCI

**R**

- Dabigatran 150mg BID + P2Y12 inhibitor
- Dabigatran 110mg BID + P2Y12 inhibitor
- Warfarin (INR 2.0-3.0) + P2Y12 inhibitor

1° End Point
Time to first clinically relevant bleeding rate (ISTH Major)

n = 2500

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* After establishing non-inferiority of the D110 and D150 DAT regimens, testing for superiority will be conducted
* ASA is discontinued immediately after a successful procedure in patients randomized to receive dabigatran
* ASA will be discontinued in the warfarin arm. BMS: Discontinuation of ASA at month 1; DES: discontinuation of ASA at month 3
* P2Y12 inhibitor (either Clopidogrel or Ticagrelor). The P2Y12 Inhibitor can be discontinued after month 12 if follow up at the discretion of the physician.
Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

**Inclusion**
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

**Randomize**

- *n = 4,600 Patients*

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

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**Apixaban**

- ASA
- placebo

**Warfarin**

- ASA
- placebo

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

**Primary outcome:** major/clinically relevant bleeding (through 6 months)
**Secondary objective:** Death, MI, stroke, stent thrombosis

[Mount Sinai Heart logo]
XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI

- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

*XARELTO® dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d).

Data on File. Janssen Pharmaceuticals, Inc.
# PIONEER vs WOEST

<table>
<thead>
<tr>
<th>Population</th>
<th>PIONEER</th>
<th>WOEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-valvular <strong>AF Pt</strong> undergoing PCI</td>
<td>Pt taking <strong>OAC</strong> &amp; undergoing PCI</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2,124</td>
<td>573</td>
</tr>
<tr>
<td><strong>Inc. criteria</strong></td>
<td>1/ <strong>Documented AF (100%)</strong> 2/ PCI</td>
<td>1/ Indication for OAC of ≥ 1 year</td>
</tr>
<tr>
<td></td>
<td><strong>Shorter Duration DAPT</strong> as Part of Triple Therapy</td>
<td>a/ <strong>AF (69%)</strong></td>
</tr>
<tr>
<td></td>
<td>Physicians could treat with DAPT for 1 or 6 months instead of 12 months</td>
<td>b/ Mechanical Valve (10%)</td>
</tr>
<tr>
<td></td>
<td>2/3rds of participants continued DAPT for 12 months</td>
<td>c/ Other (20%)</td>
</tr>
<tr>
<td><strong>DAPT</strong></td>
<td></td>
<td><strong>Longer Duration DAPT</strong> as Part of Triple Therapy</td>
</tr>
</tbody>
</table>
In an area of limited evidence, rivaroxaban is the **first** and currently **only** NOAC (versus VKA) to provide data from a dedicated RCT for patients with AF undergoing PCI.
PIioneer AF-PCI
Rationale and Design Summary

**Rationale**
- Patients with AF undergoing PCI have an indication for both OAC and antiplatelet therapy\(^1\),\(^2\) but combining a VKA with DAPT is known to be associated with an increased risk of serious bleeding episodes\(^3\).

**Objective**
- PIioneer AF-PCI is designed to assess the risk of bleeding complications with two **rivaroxaban** treatment strategies in patients with AF after PCI, compared with the standard of care\(^4\).

**Implication**
- PIioneer AF-PCI is the first randomized study to assess the **safety** of treatment strategies involving a NOAC in patients with NVAF undergoing PCI.

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Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

**Design:** An open-label, randomized, controlled phase IIIb safety study

**Population:**
patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

N=2,124

**Decision for DAPT duration:**
1, 6 or 12 months

1:1:1

Rivaroxaban 15 mg OD**# plus single antiplatelet‡

Rivaroxaban 2.5 mg BID¶ plus DAPT§

VKA (INR 2.0–3.0)¶

VKA plus low-dose ASA

Rivaroxaban 15 mg OD* plus low-dose ASA

DAPT duration (1, 6 or 12 months)

End of treatment (12 months)

---

*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

Rivaroxaban 15 mg OD: A Reduced Dose Tested For Special AF Patient Populations

<table>
<thead>
<tr>
<th>Patient populations</th>
<th>Supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with moderate renal impairment</td>
<td></td>
</tr>
<tr>
<td>(CrCl 30-49 ml/min)</td>
<td>Rocket-AF(^1)</td>
</tr>
<tr>
<td></td>
<td>n=1,474</td>
</tr>
<tr>
<td></td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Xantus(^2)</td>
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<tr>
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<td>n=1,410</td>
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<td>✓</td>
</tr>
<tr>
<td></td>
<td>PMSS(^3)</td>
</tr>
<tr>
<td></td>
<td>n=6,034*</td>
</tr>
<tr>
<td></td>
<td>✓</td>
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<tr>
<td>Japanese patients</td>
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<td></td>
<td>J-Rocket(^4)</td>
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<td></td>
<td>n=639</td>
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<tr>
<td></td>
<td>✓</td>
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<tr>
<td></td>
<td>Xapass(^5)</td>
</tr>
<tr>
<td></td>
<td>n=4,909</td>
</tr>
<tr>
<td></td>
<td>✓</td>
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<tr>
<td>Patients undergoing PCI(#)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIONEER AF-PCI(^6)</td>
</tr>
<tr>
<td></td>
<td>n=696</td>
</tr>
<tr>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*Patients with renal dysfunction (as surrogate)

#The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved

Rivaroxaban + DAPT Bleeding

Clinically Significant Bleeding (%)


Total Daily Dose:
- Rivaroxaban 20 mg ----
- Rivaroxaban 15 mg ----
- Rivaroxaban 10 mg ----
- Rivaroxaban 5 mg ----
- Placebo ----

Gibson CM, AHA 2008

Fatal Bleeding

P=0.018

Gibson CM, AHA 2011

STEMI cohort, p=0.044 in all ACS
The WOEST study showed oral anticoagulation in combination with clopidogrel was associated with significantly lower bleeding than triple therapy with no increase in thrombotic events.

This strategy has not yet been tested in a large study.

Where US guidelines recommend triple therapy with a VKA, recent European guidelines suggest that a NOAC may be used in triple and dual therapy after PCI.

Triple therapy with a VKA plus DAPT followed by dual therapy with VKA plus ASA is the standard of care for patients with AF and ACS, as recommended by US guidelines.

PIONEER AF-PCI
Rationale for Anticoagulant Dose Selection

**Study group 1**
12 months
Rivaroxaban 15 mg OD plus P2Y\textsubscript{12}

**Study group 2**
1, 6 or 12 months
Rivaroxaban 2.5 mg BID plus ASA plus P2Y\textsubscript{12}
Rivaroxaban 15 mg OD plus ASA

**Study group 3**
1, 6 or 12 months
VKA plus ASA plus P2Y\textsubscript{12}
VKA plus ASA

---

ATLAS ACS TIMI 46: rivaroxaban 15 mg OD was associated with lower bleeding rates than 20 mg OD when taken in combination with antiplatelets\textsuperscript{1}

J-ROCKET AF: rivaroxaban 15 mg OD showed similar efficacy and safety compared with warfarin, with a trend towards a lower incidence of stroke/SE\textsuperscript{2}

The safety of the rivaroxaban 2.5 mg BID dose in combination with DAPT was demonstrated in the ATLAS ACS 2 TIMI 51 trial\textsuperscript{3}

A target INR of 2.0–3.0 was selected because this is the recommended INR for stroke prevention in patients with AF\textsuperscript{4}

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**PIONEER AF-PCI**

**Rationale for Selection of ASA or P2Y$_{12}$ Inhibitor**

**Study group 1**
- 12 months
- Rivaroxaban 15 mg OD plus P2Y$_{12}$

**Study group 2**
- 1, 6 or 12 months
- Rivaroxaban 2.5 mg BID plus ASA plus P2Y$_{12}$

**Study group 3**
- 1, 6 or 12 months
- Up to 12 months
- VKA plus ASA plus P2Y$_{12}$
- Up to 12 months
- VKA plus ASA

WOEST showed that combining an OAC (VKA) and **clopidogrel** was safe and effective.

Prasugrel and ticagrelor were permitted at the discretion of the investigator as they are recommended in ACS guidelines.

In Groups 2 and 3, a period of triple therapy was followed by dual therapy using an OAC plus **low-dose ASA**.

ASA was selected over clopidogrel because it is used for long-term therapy after PCI (guidelines from the ACCF/AHA/SCAI for the management of PCI recommend continuing therapy with ASA indefinitely).

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Primary safety outcomes

- TIMI clinically significant bleeding:
  - Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention
- Time to the first event in the composite outcome
Secondary safety and efficacy outcomes

- Components of the clinically significant bleeding outcome
  - TIMI major
  - TIMI minor
  - Bleeding requiring medical attention

- Composite and components of major adverse CV events:
  - CV death
  - MI
  - Stroke

- Stent thrombosis

- Time to the first event in the composite outcome or components

Gibson CM et al, Am Heart J 2015;169:472–478e5
**PIioneer AF-PCI**

**Key Inclusion and Exclusion Criteria**

**Key inclusion criteria**
- Medical history of paroxysmal, persistent or permanent NVAF
- Undergone PCI with stent placement for primary atherosclerotic disease
- INR ≤2.5 at randomization

**Key exclusion criteria**
- Contraindication for anticoagulant or antiplatelet therapy or unacceptable risk of bleeding*
- History of stroke or TIA
- CrCl <30 ml/min at screening

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*Including, but not limited to, platelet count <90,000/μl at screening, history of ICH, 12-month history of clinically significant GI bleeding, non-VKA-induced elevated PT at screening, anaemia of unknown cause with a haemoglobin level <10 g/dl (<6.21 mmol/l) or significant liver disease or liver function test abnormalities

**PIONEER AF-PCI**

**Study Flow**

![Study Flow Diagram]

- 2,236 screened
- 112 not eligible
- 2,124 enrolled

- **709** randomized to Group 1
  - 696 received ≥1 dose
    - No DAPT stratification
  - 696 in safety analysis
  - 694 in efficacy analysis*

- **709** randomized to Group 2
  - 706 received ≥1 dose
    - 1 month DAPT: 108
    - 6 months DAPT: 248
    - 12 months DAPT: 350
  - 706 in safety analysis
  - 704 in efficacy analysis*

- **706** randomized to Group 3
  - 697 received ≥1 dose
    - 1 month DAPT: 113
    - 6 months DAPT: 243
    - 12 months DAPT: 341
  - 697 in safety analysis
  - 695 in efficacy analysis*

*Some patients excluded due to site violation of GCP guideline; no patients were lost to follow-up

More Patients in the VKA Group Discontinued Treatment Early than in Either Rivaroxaban Group

Early discontinuations were highest in the VKA plus DAPT group; discontinuation due to patient decision was significantly higher in this group vs both rivaroxaban groups.

There were no patients lost to follow up.

VKA + DAPT Regimen Discontinuation

78% have dropped antiplatelet & are in “WOEST-like” winning arm for last 6 months

WOEST
69% AF
VKA + DAPT

PIONEER AF-PCI
100% AF
VKA + DAPT

≈ 66.5%

≈ 22%

Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

**Design:** An open-label, randomized, controlled phase IIIb safety study

**Population:** patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

**Decision for DAPT duration:** 1, 6 or 12 months

- Rivaroxaban 15 mg OD*# plus single antiplatelet‡
- Rivaroxaban 2.5 mg BID¶ plus DAPT§
- Rivaroxaban 15 mg OD* plus low-dose ASA
- VKA (INR 2.0–3.0)¶ plus DAPT§
- VKA plus low-dose ASA

**DAPT duration** (1, 6 or 12 months)

**End of treatment** (12 months)

- DAPT 1 m: 15%
  6 m: 35%
  12 m: 50%
- DAPT 1 m: 16%
  6 m: 35%
  12 m: 49%

---

*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

Patients were enrolled at 431 sites across 26 countries.
Baseline Demographics Were Similar Between Groups (1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 Rivaroxaban 15 mg OD plus single antiplatelet (N=709)</th>
<th>Group 2 Rivaroxaban 2.5 mg BID plus DAPT (N=709)</th>
<th>Group 3 VKA plus DAPT (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>70.4±9.1</td>
<td>70.0±9.1</td>
<td>69.9±8.7</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>181 (25.5)</td>
<td>174 (24.5)</td>
<td>188 (26.6)</td>
</tr>
<tr>
<td>CrCl, ml/min, mean ± SD</td>
<td>78.3±31.3</td>
<td>77.5±31.8</td>
<td>80.7±30.0</td>
</tr>
<tr>
<td>≥30–&lt;60 ml/min, n (%)</td>
<td>194 (28.8)</td>
<td>196 (28.8)</td>
<td>175 (26.2)</td>
</tr>
<tr>
<td>&lt;30 ml/min, n (%)</td>
<td>8 (1.2)</td>
<td>7 (1.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2}-VASc score, mean ± SD*</td>
<td>3.73±1.69</td>
<td>3.78±1.62</td>
<td>3.82±1.55</td>
</tr>
<tr>
<td>0–1, n (%)</td>
<td>77 (10.9)</td>
<td>75 (10.6)</td>
<td>51 (7.2)</td>
</tr>
<tr>
<td>≥2, n (%)</td>
<td>632 (89.1)</td>
<td>634 (89.4)</td>
<td>655 (92.8)</td>
</tr>
<tr>
<td>HAS-BLED score, mean ± SD*</td>
<td>3.00±0.91</td>
<td>2.92±0.96</td>
<td>2.99±0.91</td>
</tr>
<tr>
<td>0–2, n (%)</td>
<td>196 (27.6)</td>
<td>227 (32.0)</td>
<td>208 (29.3)</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>513 (72.4)</td>
<td>482 (68.0)</td>
<td>498 (70.5)</td>
</tr>
<tr>
<td>Type of AF, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>146 (20.6)</td>
<td>146 (20.6)</td>
<td>149 (21.1)</td>
</tr>
<tr>
<td>Permanent</td>
<td>262 (37.0)</td>
<td>238 (33.6)</td>
<td>243 (34.5)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>300 (42.4)</td>
<td>325 (45.8)</td>
<td>313 (44.4)</td>
</tr>
</tbody>
</table>

*Values calculated from data in published manuscript (not explicitly stated)
Baseline Demographics Were Similar Between Groups (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1: Rivaroxaban 15 mg OD plus single antiplatelet (N=709)</th>
<th>Group 2: Rivaroxaban 2.5 mg BID plus DAPT (N=709)</th>
<th>Group 3: VKA plus DAPT (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2Y₁₂ inhibitor at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>660 (93.1)</td>
<td>664 (93.7)</td>
<td>680 (96.3)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>12 (1.7)</td>
<td>11 (1.6)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>37 (5.2)</td>
<td>34 (4.8)</td>
<td>21 (3.0)</td>
</tr>
<tr>
<td>Urgency of revascularization, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>428 (60.4)</td>
<td>430 (60.6)</td>
<td>449 (63.6)</td>
</tr>
<tr>
<td>Urgent</td>
<td>281 (39.6)</td>
<td>279 (39.4)</td>
<td>257 (36.4)</td>
</tr>
<tr>
<td>Type of index event, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>130 (18.5)</td>
<td>129 (18.4)</td>
<td>123 (17.8)</td>
</tr>
<tr>
<td>STEMI</td>
<td>86 (12.3)</td>
<td>97 (13.8)</td>
<td>74 (10.7)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>145 (20.7)</td>
<td>148 (21.1)</td>
<td>164 (23.7)</td>
</tr>
<tr>
<td>Type of stent, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>464 (65.4)</td>
<td>471 (66.8)</td>
<td>468 (66.5)</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>231 (32.6)</td>
<td>220 (31.2)</td>
<td>224 (31.8)</td>
</tr>
<tr>
<td>Both</td>
<td>14 (2.0)</td>
<td>14 (2.0)</td>
<td>12 (1.7)</td>
</tr>
</tbody>
</table>

Time in Therapeutic Range When Receiving VKA plus DAPT Was High Across All Participating Regions

- Average TTR (INR 2.0–3.0) was 65%

TTR by region (safety analysis set)

Both Rivaroxaban Strategies was Associated With Significantly Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001

Primary Safety Endpoint: Reduced with Rivaroxaban Strategies vs VKA

- Group 3 (VKA plus DAPT) (n=697)
- Group 2 (rivaroxaban 2.5 mg BID plus DAPT) (n=706)
- Group 1 (rivaroxaban 15 mg OD plus single antiplatelet) (n=696)

360-day Kaplan-Meier estimate (%)

- Clinically significant bleeding
- TIMI major
- TIMI minor
- Bleeding requiring medical attention

Both rivaroxaban strategies associated with significant reduction in incidence of clinically significant bleeding vs the VKA plus DAPT strategy

*p=0.002 vs Group 3; **p<0.001 vs Group 3; *composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

Primary Safety Endpoint: Reduced with Rivaroxaban Strategies vs VKA

- Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT
  - HR=0.59
  - (95% CI 0.47–0.76)
  - p<0.001

- Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT
  - HR=0.63
  - (95% CI 0.50–0.80)
  - p<0.001

ARR
- 26.7% NNT=12
- 18.0% ARR 8.7% NNT=11
- 16.8% ARR 9.9%

Group 3 (VKA plus DAPT)
Group 2 (Rivaroxaban 2.5 mg BID plus DAPT)
Group 1 (Rivaroxaban 15 mg OD plus single antiplatelet)

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>180</th>
<th>270</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>696</td>
<td>628</td>
<td>606</td>
<td>585</td>
<td>543</td>
<td>510</td>
<td>383</td>
<td></td>
</tr>
<tr>
<td>706</td>
<td>636</td>
<td>600</td>
<td>579</td>
<td>543</td>
<td>509</td>
<td>409</td>
<td></td>
</tr>
<tr>
<td>697</td>
<td>593</td>
<td>555</td>
<td>521</td>
<td>461</td>
<td>426</td>
<td>329</td>
<td></td>
</tr>
</tbody>
</table>

Both rivaroxaban strategies associated with significant reduction in incidence of clinically significant bleeding vs the VKA plus DAPT strategy

**ISTH Major Bleeding Significantly Reduced with Rivaroxaban Strategies vs VKA**

*Both rivaroxaban strategies associated with significant reduction in ISTH major and clinically relevant non-major bleeding vs the VKA plus DAPT strategy*

- Group 3 (VKA plus DAPT) (n=697)
- Group 2 (rivaroxaban 2.5 mg BID plus DAPT (n=706)
- Group 1 (rivaroxaban 15 mg OD plus single antiplatelet) (n=696)

**Incidence of fatal bleeding:** 0.3% in group 1, 0.3% in group 2, 0.9% in group 3

*p<0.05 vs Group 3*

# ISTH Major Bleeding Significantly Reduced with Rivaroxaban Strategies vs VKA

<table>
<thead>
<tr>
<th>ISTH classification</th>
<th>Incidence (%)</th>
<th>Group 1 vs Group 3 (rivaroxaban plus single antiplatelet vs VKA plus DAPT) p-value</th>
<th>Group 2 vs Group 3 (rivaroxaban plus DAPT vs VKA plus DAPT) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (N=696)</td>
<td>Group 2 (N=706)</td>
<td>Group 3 (N=697)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>27 (3.9)</td>
<td>25 (3.5)</td>
<td>48 (6.9)</td>
</tr>
<tr>
<td>Haemoglobin drop*</td>
<td>21 (3.0)</td>
<td>19 (2.7)</td>
<td>34 (4.9)</td>
</tr>
<tr>
<td>Transfusion*</td>
<td>15 (2.2)</td>
<td>13 (1.8)</td>
<td>15 (2.2)</td>
</tr>
<tr>
<td>Critical organ bleeding†</td>
<td>6 (0.9)</td>
<td>5 (0.7)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>90 (12.9)</td>
<td>97 (13.7)</td>
<td>130 (18.7)</td>
</tr>
<tr>
<td>Minimal bleeding</td>
<td>123 (17.7)</td>
<td>151 (21.4)</td>
<td>163 (23.4)</td>
</tr>
</tbody>
</table>

Both rivaroxaban strategies associated with significant reduction in ISTH major and clinically relevant non-major bleeding vs the VKA plus DAPT strategy

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*Fall in haemoglobin ≥2 g/dl; †transfusion of ≥2 units of packed red blood cells or whole blood; ‡investigator-reported bleeding from one of the following sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
Primary Safety Endpoint Reduced with Rivaroxaban vs VKA Irrespective of DAPT Duration

 grupos 2 and 3 were stratified according to the intended duration of triple therapy (decided by the physician before randomization)

Clinically significant bleeding according to DAPT duration

The rivaroxaban treatment strategy (2.5 mg BID plus DAPT followed by 15 mg OD plus ASA) reduced bleeding risk vs the VKA plus DAPT strategy irrespective of DAPT duration

*p<0.01 vs VKA plus DAPT

## Bleeding Events using GUSTO & BARC Scales (Pre-specified Secondary Analyses)

<table>
<thead>
<tr>
<th></th>
<th>Riva + P2Y₁₂ (N=696)</th>
<th>Riva + DAPT (N=706)</th>
<th>Combined Riva (N=1402)</th>
<th>VKA + DAPT (N=697)</th>
<th>Group 1 vs Group 3 p-value</th>
<th>Group 2 vs Group 3 p-value</th>
<th>Combined vs Group 3 p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTO classification, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7 (1.0)</td>
<td>10 (1.4)</td>
<td>17 (1.2)</td>
<td>20 (2.9)</td>
<td><strong>0.012</strong></td>
<td>0.060</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (1.9)</td>
<td>10 (1.4)</td>
<td>23 (1.6)</td>
<td>9 (1.3)</td>
<td>0.388</td>
<td>0.839</td>
<td>0.539</td>
</tr>
<tr>
<td>Mild</td>
<td>193 (27.7)</td>
<td>214 (30.3)</td>
<td>407 (29.0)</td>
<td>255 (36.6)</td>
<td><strong>&lt;0.001</strong></td>
<td>0.013</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>BARC classification, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 0</td>
<td>9 (1.3)</td>
<td>14 (2.0)</td>
<td>23 (1.6)</td>
<td>10 (1.4)</td>
<td>0.820</td>
<td>0.428</td>
<td>0.721</td>
</tr>
<tr>
<td>Type 1 (minimal)</td>
<td>125 (18.0)</td>
<td>153 (21.7)</td>
<td>278 (19.8)</td>
<td>167 (24.0)</td>
<td><strong>0.006</strong></td>
<td>0.307</td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>Type 2 (actionable)</td>
<td>92 (13.2)</td>
<td>91 (12.9)</td>
<td>183 (13.1)</td>
<td>126 (18.1)</td>
<td><strong>0.013</strong></td>
<td><strong>0.007</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Type 3a</td>
<td>8 (1.2)</td>
<td>7 (1.0)</td>
<td>15 (1.1)</td>
<td>12 (1.7)</td>
<td>0.369</td>
<td>0.237</td>
<td>0.212</td>
</tr>
<tr>
<td>Type 3b (&gt;5g, pressors)</td>
<td>13 (1.9)</td>
<td>16 (2.3)</td>
<td>29 (2.1)</td>
<td>26 (3.7)</td>
<td><strong>0.035</strong></td>
<td>0.108</td>
<td><strong>0.025</strong></td>
</tr>
<tr>
<td>Type 3c</td>
<td>2 (0.3)</td>
<td>5 (0.7)</td>
<td>7 (0.5)</td>
<td>4 (0.6)</td>
<td>0.687</td>
<td>&gt;0.999</td>
<td>0.760</td>
</tr>
<tr>
<td>Type 4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type 5a (probable fatal)*</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>&gt;0.999</td>
<td>0.497</td>
<td>0.554</td>
</tr>
<tr>
<td>Type 5b (definite fatal)#</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
<td>3 (0.2)</td>
<td>7 (1.0)</td>
<td>0.070</td>
<td>0.106</td>
<td><strong>0.019</strong></td>
</tr>
</tbody>
</table>

Note: Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
*Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging; #Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy

BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization Of Streptokinase and Tpa For Occluded Arteries

Efficacy was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

Comparable Efficacy with Rivaroxaban Strategies vs VKA plus DAPT

Components of composite endpoint and stent thrombosis

Incidence of major adverse CV events was comparable between all three treatment strategies; however, the trial was not powered for efficacy

*Composite of CV death, MI and stroke

Components of composite endpoint and stent thrombosis

- Group 3 (VKA plus DAPT) (n=695)
- Group 2 (rivaroxaban 2.5 mg BID plus DAPT) (n=704)
- Group 1 (rivaroxaban 15 mg OD plus single antiplatelet) (n=694)
# Major Adverse Cardiac Events
## All Strata

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimates</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
</tr>
<tr>
<td>Riva + P2Y12</td>
<td>1.08 (0.69-1.68)</td>
</tr>
<tr>
<td>(N=694)</td>
<td>p=0.750</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>1.29 (0.59-2.80)</td>
</tr>
<tr>
<td>(N=704)</td>
<td>p=0.523</td>
</tr>
<tr>
<td>VKA + DAPT</td>
<td>0.86 (0.46-1.59)</td>
</tr>
<tr>
<td>(N=695)</td>
<td>p=0.625</td>
</tr>
<tr>
<td></td>
<td><strong>Riva + DAPT</strong> vs. VKA + DAPT</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse CV Event</td>
<td>1.08 (0.69-1.68)</td>
</tr>
<tr>
<td>41 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>1.29 (0.59-2.80)</td>
</tr>
<tr>
<td>15 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.86 (0.46-1.59)</td>
</tr>
<tr>
<td>19 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 (0.39-2.96)</td>
</tr>
<tr>
<td>8 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>1.20 (0.32-4.45)</td>
</tr>
<tr>
<td>5 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Adverse CV Events + Stent Thrombosis</td>
<td>1.08 (0.69-1.68)</td>
</tr>
<tr>
<td>41 (6.5%)</td>
<td></td>
</tr>
</tbody>
</table>

### Notes:
- Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
- A subject could have more than component event. n = number of subjects with events, N = number of subjects at risk, % = KM estimate at the end of study.
- Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg OD comparing VKA) Cox proportional hazards model.
- Log-Rank p-values as compared to VKA group are based on the (stratified, only for Overall 2.5 mg BID/15 mg OD comparing VKA) two-sided log rank test.
- CI = confidence interval, DAPT = dual antiplatelet therapy, HR = hazard ratio, VKA = vitamin K antagonist
- 6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines.
Trial was not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

- Power to detect a $\geq 15\%$ risk reduction for major adverse CV events was 11.4\%
- Assuming a 90\% power to detect a 15\% relative difference between the treatment groups, a superiority trial would require 13,598 participants/arm
How Many Patients Would it Take to Show Difference?

This trial has several limitations. First, the secondary analyses showed that the efficacy of each of the two doses of rivaroxaban was similar to that of standard therapy. However, the number of secondary efficacy end points in this study was small, and the trial was not powered to definitively establish either superiority or noninferiority. Using the rate for a major adverse cardiovascular event observed in the standard-therapy group of 6.0%, and assuming 90% power to detect a difference between the treatment groups of 15 percentage points at an alpha level of 0.05, we calculate that the sample size needed for a superiority trial would be 13,598 participants per group (a total of 40,794 participants across three groups). Because enrollment and follow-up in this trial involving only 2100 participants at 431 sites required 3 years, the feasibility of enrolling more than 20 times the number of participants over such a protracted period of time is questionable.
**Related Studies Provide Further Supportive Data but are Also Not Powered for Efficacy**

<table>
<thead>
<tr>
<th>OAC</th>
<th>Study name (Trial ID)</th>
<th>Sample size</th>
<th>Treatment Arms</th>
</tr>
</thead>
</table>
| Rivaroxaban (China only)   | RT-AF (NCT02334254)   | 420*        | • Rivaroxaban 2.5mg or 5mg BID plus ticagrelor 90mg BID  
  • Aspirin 100mg OD, clopidogrel 75mg OD, plus warfarin (INR 1.8-2.5) |
| Rivaroxaban (Japan only)   | AFIRE (NCT02642419)   | 2200*       | • Rivaroxaban 15mg/10mg OD  
  • Rivaroxaban plus single antiplatelet drug: aspirin 81mg or 100mg OD, clopidogrel 75mg/50mg OD or prasugrel 3.75/2.5mg OD |
| Apixaban                   | AUGUSTUS (NCT02415400) | 4600*       | • Apixaban 5/2.5mg BID | VKA  
  • Aspirin 81mg OD | placebo |
| Edoxaban                   | ENTRUST AF-PCI (NCT02866175) | 1500*       | • Edoxaban 60/30mg OD  
  • VKA OD plus clopidogrel 75mg OD or with documented clinical need: prasugrel 10/5mg OD or ticagrelor 90mg BID |
| Dabigatran                 | REDUAL-PCI (NCT02164864) | 2800*       | • Dabigatran 110mg or 150 mg BID plus clopidogrel or ticagrelor  
  • Warfarin OD plus aspirin and clopidogrel or ticagrelor |
| All anticoagulants (US only)| The AVIATOR 2 Registry (NCT02362659) | 2500*       | • Antiplatelet plus anticoagulant  
  • DAPT alone  
  • DAPT plus anticoagulant |
| All OACs (Japan only)      | OAC-ALONE (NCT01962545) | 2000*       | • OAC alone: warfarin or NOAC  
  • OAC plus single antiplatelet |

*Estimated enrolment
Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies of Rivaroxaban or a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy

BACKGROUND: Patients with atrial fibrillation who undergo intracoronary stenting traditionally are treated with a vitamin K antagonist (VKA) plus dual antiplatelet therapy (DAPT), yet this treatment leads to high risks of bleeding. We hypothesized that a regimen of rivaroxaban plus a P2Y12 inhibitor monotherapy or rivaroxaban plus DAPT could reduce bleeding and thereby have a favorable impact on all-cause mortality and the need for rehospitalization.

METHODS: Stented subjects with nonvalvular atrial fibrillation (n=2124) were randomized 1:1:1 to administration of reduced-dose rivaroxaban 15 mg daily plus a P2Y12 inhibitor for 12 months (group 1); rivaroxaban 2.5 mg twice daily with stratification to a prespecified duration of DAPT of 1, 6, or 12 months (group 2); or the reference arm of dose-adjusted VKA daily with a similar DAPT stratification (group 3). The present post hoc analysis assessed the end point of all-cause mortality or recurrent hospitalization for an adverse event, which was further classified as the result of bleeding, a cardiovascular, or another cause blinded to treatment assignment.

RESULTS: The risk of all-cause mortality or recurrent hospitalization was 34.9% in group 1 (hazard ratio=0.79; 95% confidence interval, 0.66–0.94; P=0.008 versus group 3; number needed to treat=15), 31.9% in group 2 (hazard ratio=0.75; 95% confidence interval, 0.62–0.90; P=0.002 versus group 3; number needed to treat=10), and 41.9% in group 3 (VKA+DAPT). Both all-cause death plus hospitalization potentially resulting from bleeding (group 1=8.6%; P=0.032 versus group 3), group 2=8.0% (P=0.012 versus group 3), and group 3=12.4%) and all-cause death plus rehospitalization potentially resulting from a cardiovascular cause (group 1=21.4% [P=0.001 versus group 3], group 2=21.7% [P=0.011 versus group 3], and group 3=29.3%) were reduced in the rivaroxaban arms compared with the VKA arm, but other forms of rehospitalization were not.

CONCLUSIONS: Among patients with atrial fibrillation undergoing intracoronary stenting, administration of either rivaroxaban 15 mg daily plus P2Y12 inhibitor monotherapy or 2.5 mg rivaroxaban twice daily plus DAPT was associated with a reduced risk of all-cause mortality or recurrent hospitalization for adverse events compared with standard-of-care VKA plus DAPT.

All Cause Hospitalization for an Adverse Event

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.
Re-hospitalization Due to CV Events and Bleeding Were Both Reduced with the Rivaroxaban Strategies

Adverse events leading to hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes; Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Gibson CM et al, Circulation 2016; doi:10.1161/CIRCULATIONAHA.116.025783
Considering Practical Use, Rivaroxaban 15 mg OD Plus Antiplatelet Could Become Approach of Choice*

Illustrative example of practical implications for an AF patient

*The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved
Canadian Cardiovascular Society Guidelines Recommend OAC + single AP after Elective PCI

For patients with AF and recent elective PCI

Age <65 and CHADS\(_2\) =0

ASA plus clopidogrel for 12 months

ASA alone after 12 months

Age ≥65 or CHADS\(_2\) ≥1

OAC* plus clopidogrel for 12 months

OAC* alone after 12 months

*A NOAC is preferred over warfarin for patients with NVAF

et al, Can J Cardiol 2016;32:1170–1185
O PIONEERs!
The Beginning of the End of Full-Dose Triple Therapy with Warfarin?

Deepak L. Bhatt, MD, MPH
1. In an area of limited evidence, rivaroxaban is the first and currently only NOAC (vs VKA) to provide data from a dedicated RCT for patients with AF undergoing PCI*1

2. In PIONEER AF-PCI, rivaroxaban 15 mg OD plus single antiplatelet therapy demonstrated significantly improved safety vs VKA plus DAPT.

3. In PIONEER AF-PCI, rivaroxaban 15 mg OD plus single antiplatelet therapy demonstrated comparable efficacy vs VKA plus DAPT was observed, however, the trial was not powered to definitively demonstrate either superiority or non-inferiority for efficacy¹

4. Considering both safety and practical use, the reduced dose of rivaroxaban 15 mg OD plus single antiplatelet therapy could become the approach of choice¹

PIONEER AF-PCI

Back-Up and Administrative Information
A randomized trial for DAPT (n=3,335) vs VKA (n=3,371) for prevention of vascular events in patients with AF demonstrated superiority of OAC therapy.

RR=1.44 (95% CI 1.18–1.76)

*p=0.0003

Primary efficacy outcome* (%/year)

VKA (INR 2.0–3.0)

DAPT (75 mg clopidogrel plus 75–100 mg ASA)

3,9

5,6

*Composite of stroke, non-CNS embolus, MI and vascular death

The ACTIVE Writing Group. Lancet 2006;367:1903–1912
### Primary Safety Endpoint: Reduced with Rivaroxaban Strategies vs VKA

**Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant bleeding</td>
<td>0.59</td>
<td>0.46–0.75</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major</td>
<td>0.66</td>
<td>0.33–1.31</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>0.51</td>
<td>0.20–1.28</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>BRMA</td>
<td>0.61</td>
<td>0.47–0.80</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant bleeding</td>
<td>0.63</td>
<td>0.50–0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major</td>
<td>0.57</td>
<td>0.28–1.16</td>
<td>0.11</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>0.50</td>
<td>0.20–1.26</td>
<td>0.13</td>
</tr>
<tr>
<td>BRMA</td>
<td>0.67</td>
<td>0.52–0.86</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Both rivaroxaban strategies were associated with a significant reduction in the incidence of clinically significant bleeding vs the VKA plus DAPT strategy.
Primary Safety Endpoint Reduced with Rivaroxaban vs VKA Irrespective of DAPT Duration

- Groups 2 and 3 were stratified according to the intended duration of triple therapy (decided by the physician before randomization)

Clinically significant bleeding according to DAPT duration

The rivaroxaban treatment strategy (2.5 mg BID plus DAPT followed by 15 mg OD plus ASA) reduced bleeding risk vs the VKA plus DAPT strategy irrespective of DAPT duration

*\(p<0.01\) vs VKA plus DAPT

### Comparable Efficacy with Rivaroxaban Strategies vs VKA plus DAPT

#### Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse CV events*</td>
<td>1.08</td>
<td>0.69–1.68</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>CV death</td>
<td>1.29</td>
<td>0.59–2.80</td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>MI</td>
<td>0.86</td>
<td>0.46–1.59</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07</td>
<td>0.39–2.96</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.20</td>
<td>0.32–4.45</td>
<td></td>
<td>0.79</td>
</tr>
</tbody>
</table>

#### Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse CV events*</td>
<td>0.93</td>
<td>0.59–1.48</td>
<td>0.77</td>
</tr>
<tr>
<td>CV death</td>
<td>1.19</td>
<td>0.54–2.62</td>
<td>0.66</td>
</tr>
<tr>
<td>MI</td>
<td>0.75</td>
<td>0.40–1.42</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.36</td>
<td>0.52–3.58</td>
<td>0.53</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.44</td>
<td>0.40–5.09</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Incidence of major adverse CV events was comparable between all three treatment strategies; however the trial was not powered for efficacy.

*Composite of CV death, MI and stroke

Comparable Efficacy with Rivaroxaban plus DAPT vs VKA plus DAPT Irrespective of DAPT Duration

Major adverse CV events* according to DAPT duration

No significant differences in major adverse CV events were observed irrespective of DAPT duration (note that the study was not powered for efficacy, and baseline characteristics are not balanced within each DAPT stratum)

*Composite of CV death, MI and stroke
### Time to the First Occurrence of Overall Stroke and its Components

<table>
<thead>
<tr>
<th></th>
<th>Kaplan-Meier Estimates</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt; (N=694)</td>
<td>Riva + DAPT (N=704)</td>
</tr>
<tr>
<td>Overall Stroke</td>
<td>8 (1.3%)</td>
<td>10 (1.5%)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>7 (1.2%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with Hemorrhagic Transformation</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Uncertain Stroke</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Primary Hemorrhagic Stroke</td>
<td>1 (0.2%)</td>
<td>2 (0.3%)</td>
</tr>
</tbody>
</table>

MATCH: ASA + Clopidogrel Versus Clopidogrel after Ischaemic Stroke/TIA

![Graph showing cumulative event rate over time for Placebo and clopidogrel vs. ASA and clopidogrel. The p-value is 0.244.]

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>3797</th>
<th>3576</th>
<th>3440</th>
<th>3321</th>
<th>3229</th>
<th>3130</th>
<th>2441</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA + clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + clopidogrel</td>
<td>3802</td>
<td>3576</td>
<td>3439</td>
<td>3326</td>
<td>3200</td>
<td>3119</td>
<td>2446</td>
</tr>
</tbody>
</table>
### MATCH: ASA + Clopidogrel Versus Clopidogrel after Ischaemic Stroke/TIA

#### Number (%) of patients with bleeding events

<table>
<thead>
<tr>
<th>Event</th>
<th>ASA and clopidogrel (n=3759)</th>
<th>Placebo and clopidogrel (n=3781)</th>
<th>Difference (%) between ASA and placebo (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening bleeding</td>
<td>96 (3)</td>
<td>49 (1)</td>
<td>1.26 (0.64–1.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>16 (&lt;1)</td>
<td>11 (&lt;1)</td>
<td>0.13 (-0.14–0.40)</td>
<td></td>
</tr>
<tr>
<td>Non-fatal bleeding</td>
<td>81 (2)</td>
<td>38 (1)</td>
<td>1.15 (0.59–1.71)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage†</td>
<td>40 (1)</td>
<td>25 (1)</td>
<td>0.40 (-0.01–0.82)</td>
<td></td>
</tr>
<tr>
<td>Primary intracranial haemorrhage</td>
<td>32 (1)</td>
<td>17 (&lt;1)</td>
<td>0.40 (0.04–0.76)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>73 (2)</td>
<td>22 (1)</td>
<td>1.36 (0.86–1.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>120 (3)</td>
<td>39 (1)</td>
<td>2.16 (1.51–2.81)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Pearson’s X² test; †All symptomatic (and thus primary) intracranial haemorrhages were life-threatening bleeds

[See et al. Lancet 2004;364:331–337](#)