NOAC in patients with Atrial Fibrillation and Acute Coronary Syndromes

Matteo Bertini, MD, PhD

Department of Cardiology,
Arcispedale S. Anna
University of Ferrara
Among ACS patients undergoing PCI, approximately 5% to 21% of patients have concomitant AF.

Despite overlap in the occurrence of these syndromes, the pharmacotherapies used to manage AF and ACS differ.

Rubboli et al., J Interv Cardiol 2009
Coronary stent implantation

Cardiac Events

- Oral Anticoagulation
- Dual Antiplatelet

Days after Stenting

ISAR, NEJM 1996

Atrial fibrillation

- Dual Antiplatelet
- Oral Anticoagulation

Cumulative hazard rates

RR = 1.44 (1.18-1.76), p = 0.0003

ACTIVE-W Lancet 2006

Dual Antiplatelet + Oral Anticoagulation
The management of AF patients who undergo stent placement for an ACS is challenging.
Ischaemic stroke associated with warfarin, aspirin and clopidogrel in patients with AF

n = 82854

Hansen et al. Arch Int Med 2010; 170: 1433-1441
Bleeding associated with warfarin, aspirin and clopidogrel in patients with AF

\[ n = 82854 \]

Hansen et al. Arch Int Med 2010; 170: 1433-1441
Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van ‘t Hof, Jurriën M ten Berg, for the WOEST study investigators

Lancet 2013; 381: 1107-15
Primary outcome: any bleeding episode within 1 year of PCI
ISAR-TRIPLE

- 600 pts
- Indication to VKA+DES (ACS or elective)
- 9-month follow-up
- Composite endpoint: death, MI, stroke, ST, TIMI-bleeding
**Primary Endpoint**

Death, myocardial infarction, stent thrombosis, stroke or TIMI major bleeding

HR 1.14 (95%, CI 0.68 – 1.91), p=0.63

**Secondary Endpoints**

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke

HR 0.93 (0.43 - 2.05), p=0.87

TIMI major bleeding

HR 1.35 (0.64 - 2.84), p=0.44

- **Cumulative Incidence (%)**

- **Months After Randomization**

- **6-month group**

- **6-week group**
NOACS in association with DAPT (aspirin+clopidogrel) ?

In all NOACS trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) patients were excluded from enrollment if receiving new P2Y12

And conversely, AF patients requiring OAC were systematically excluded from recent ACS trials.

Some data are available in non AF patients
97% patients were taking aspirin
81% patients were taking aspirin plus a P2Y12-receptor inhibitor (predominantly clopidogrel)
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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>48</td>
<td>1.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>18</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

HR 2.59; 95% CI 1.50–4.46; p=0.001
Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

**ATLAS ACS 2 TIMI 51**

**N=15,526*\**

**Event-driven study – 1002 events**

**Stratum 1: ASA alone (7%)**
- Placebo n=355
- Rivaroxaban 2.5 mg bid n=349
- Rivaroxaban 5 mg bid n=349

**Stratum 2: ASA + thienopyridine (93%)**
- Placebo n=4821
- Rivaroxaban 2.5 mg bid n=4825
- Rivaroxaban 5 mg bid n=4827

*Mega et al, 2011*
Primary efficacy endpoint (CV death/MI/stroke)
Both rivaroxaban doses, both strata

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months after randomization</td>
<td>0</td>
<td>5113</td>
</tr>
<tr>
<td>4</td>
<td>4307</td>
<td>8502</td>
</tr>
<tr>
<td>8</td>
<td>3470</td>
<td>6753</td>
</tr>
<tr>
<td>12</td>
<td>2664</td>
<td>5137</td>
</tr>
<tr>
<td>16</td>
<td>1831</td>
<td>3554</td>
</tr>
<tr>
<td>20</td>
<td>1079</td>
<td>2084</td>
</tr>
<tr>
<td>24</td>
<td>421</td>
<td>831</td>
</tr>
</tbody>
</table>

HR=0.84 (0.74–0.96) ARR=1.7% mITT \(p=0.008\) ITT \(p=0.002\) NNT=56

Mega et al, 2011

ATLAS ACS 2 TIMI 51
## Safety endpoint

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban 2.5 mg bid (n=5115)</th>
<th>Rivaroxaban 5 mg bid (n=5110)</th>
<th>Placebo (n=5125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-CABG TIMI major bleed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>1.8%</td>
<td>2.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>p value versus placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>p value versus placebo</td>
<td>0.04</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>p value versus placebo</td>
<td>0.45</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal ICH</strong></td>
<td></td>
<td></td>
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<tr>
<td>K–M estimate at 2 years</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>p value versus placebo</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Mega et al, 2011*
Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the RELY Trial

Event Rate (% per year)

- **Major Bleed**
  - HR = 1.87 (95% CI: 1.54, 2.27)
  - HR = 2.14 (95% CI: 1.75, 2.61)
  - HR = 2.05 (95% CI: 1.66, 2.54)

- **Minor Bleed**
  - HR = 1.47 (95% CI: 1.34, 1.62)
  - HR = 1.33 (95% CI: 1.20, 1.47)
  - HR = 1.44 (95% CI: 1.29, 1.59)

- **Extracranial Bleed**
  - HR = 1.84 (95% CI: 1.48, 2.29)
  - HR = 2.14 (95% CI: 1.74, 2.64)
  - HR = 2.07 (95% CI: 1.66, 2.59)

- **Intracranial Bleed**
  - HR = 1.85 (95% CI: 1.22, 2.82)
  - HR = 1.98 (95% CI: 1.04, 3.77)
  - HR = 1.53 (95% CI: 0.70, 3.34)

An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI)

C. Michael Gibson, MS, MD, a Roxana Mehran, MD, b Christoph Bode, MD, c Johnathan Halperin, MD, b Freek Verheugt, MD, d Peter Wildgoose, PhD, e Martin van Eickels, MD, f Gregory Y. H. Lip, MD, g Marc Cohen, MD, h Steen Husted, MD, i Eric Peterson, MD, j and Keith Fox, MD k Boston, MA; New York, NY; Freiburg, Germany; Nijmegen, the Netherlands; Titusville, Newark, NJ; Berkeley, CA; Birmingham, Edinburgh, United Kingdom; Herning, Denmark; and Durham, NC
**PIONEER AF-PCI**

- **No aspirin**
  - Rivaroxaban 15 mg/d + clopidogrel/prasugrel/ticagrelor

- **End of treatment at 12 months**
  - Rivaroxaban 2.5 mg twice daily + DAPT
  - Rivaroxaban 15 mg/d + low-dose aspirin

- **Intended DAPT duration:** 1, 6, or 12 months

- **VKA + DAPT INR 2.0-3.0**
  - VKA + low-dose aspirin

- **N=2100 1:1:1**

- **PCI (with stent placement); paroxysmal, persistent or permanent nonvalvular AF**

  - ≤ 72 hours after sheath removal, INR must be ≤ 2.5 at time of randomization

**Primary outcome measures:** clinically significant bleeding (composite of TIMI major, minor bleeding, and bleeding) requiring medical attention.

**Secondary outcome measures:** composite of CV death, MI, and stroke

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**a. DAPT = low-dose aspirin + clopidogrel, prasugrel, or ticagrelor**

ClinicalTrials.gov website.
1. PIONEER–AF-PCI is not powered to detect differences in stroke rates...

2. it will still remain uncertain if rivaroxaban 2.5 mg b.i.d. would adequately reduce strokes in AF, even when combined with antiplatelet agents...
RE-DUAL PCI™
Study in NVAF patients undergoing PCI

**STUDY TITLE**
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 plus aspirin in patients with non-valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (PCI) with stenting. (RE-DUAL PCI)

**STUDY HYPOTHESES**
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

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)

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

1st End Point
Time to first combined thrombotic event or death (all death, MI, Stroke/SE)
Plus
Time to first clinically relevant bleeding rate (ISTH Major)

n = 2840 patients per arm (Total = 8520 patients)

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- After establishing non-inferiority of the D110 and D150 DAB regimens, testing for superiority will be conducted
- ASA is discontinued immediately after a successful procedure in patients randomised 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 or follow up at the discretion of the physician
2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation
1. Personalize antithrombotic therapy according to:

- Stroke risk (CHA$_2$DS$_2$ VASC)
- Bleeding risk (HAS BLED)
- Clinical setting (ACS vs elective)
- Stent type (DES vs BMS)
- Time from PCI/ACS
In practice... what to do?

2. Prefer:

- The lower tested dose for stroke prevention in AF (that is, dabigatran 110 mg b.i.d., rivaroxaban 15 mg o.d. or apixaban 2.5 mg b.i.d.) to minimize the risks of bleeding
- Clopidogrel instead of the more potent ticagrelor and prasugrel
- New generation DES (or BMS) over first generation DES
- Use of the radial approach, thus minimizing the risk of access site bleeding
Thanks!
Oral Anticoagulation and Antiplatelets in Atrial Fibrillation Patients After Myocardial Infarction and Coronary Intervention

Morten Lamberts, MD,* † Gunnar H. Gislason, MD, PhD, †‡ Jonas Bjerring Olesen, MD,* Søren Lund Kristensen, MD,* Anne-Marie Schjerning Olsen, MD,* Anders Mikkelsen, MB,* Christine Benn Christensen, MD,* Gregory Y. H. Lip, MD, † Lars Kober, MD, DMS, †​
Christian Torp-Pedersen, MD, DMS, ‡ Morten Lock Hansen, MD, PhD

*Hellerup, Copenhagen, and Aalborg, Denmark; and Birmingham, United Kingdom

Figure 3 Benefit and Safety With Triple Therapy Versus Dual Therapies
Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS)
**Dual therapy:**
OAC + 75 mg clopidogrel

1 Month minimum after BMS
1 Year minimum after DES

**Triple therapy:**
OAC + 75 mg clopidogrel + 80 mg acetylsalicylic acid OR 100 mg carbasylate calcium

1 Month Min. after BMS
1 Year Min. after DES

[Flowchart image]
- 573 patients randomised
- 284 patients assigned double therapy
  - 7 patients excluded
    - 3 no PCI
    - 2 withdrew consent
    - 1 lost to follow-up
    - 1 did not meet inclusion criteria
  - 279 patients included in intention-to-treat analysis
- 289 patients assigned triple therapy
  - 6 patients excluded
    - 1 no PCI
    - 2 withdrew consent
    - 1 lost to follow-up
    - 2 did not meet inclusion criteria
  - 284 patients included in intention-to-treat analysis
<table>
<thead>
<tr>
<th>Event</th>
<th>Double therapy (n=279)</th>
<th>Triple therapy (n=284)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding event</td>
<td>54 (19.4%)</td>
<td>126 (44.4%)</td>
<td>0.36 (0.26–0.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>9 (3.2%)</td>
<td>16 (5.6%)</td>
<td>0.56 (0.25–1.27)</td>
<td>0.159</td>
</tr>
<tr>
<td>Major and minor</td>
<td>39 (14.0%)</td>
<td>89 (31.3%)</td>
<td>0.40 (0.27–0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GUSTO bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (1.4%)</td>
<td>10 (3.5%)</td>
<td>0.40 (0.12–1.27)</td>
<td>0.119</td>
</tr>
<tr>
<td>Severe and moderate</td>
<td>15 (5.4%)</td>
<td>35 (12.3%)</td>
<td>0.42 (0.23–0.76)</td>
<td>0.003</td>
</tr>
<tr>
<td>BARC bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 (6.5%)</td>
<td>36 (12.7%)</td>
<td>0.49 (0.28–0.86)</td>
<td>0.011</td>
</tr>
<tr>
<td>3c</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>1.00 (0.20–4.90)</td>
<td>0.996</td>
</tr>
<tr>
<td>3b</td>
<td>6 (2.2%)</td>
<td>14 (5.0%)</td>
<td>0.43 (0.17–1.10)</td>
<td>0.074</td>
</tr>
<tr>
<td>3a</td>
<td>9 (3.2%)</td>
<td>19 (6.7%)</td>
<td>0.47 (0.21–1.00)</td>
<td>0.054</td>
</tr>
<tr>
<td>2</td>
<td>23 (8.2%)</td>
<td>59 (20.8%)</td>
<td>0.36 (0.23–0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2+3</td>
<td>40 (14.3%)</td>
<td>90 (31.7%)</td>
<td>0.40 (0.28–0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>18 (6.5%)</td>
<td>45 (15.8%)</td>
<td>0.38 (0.22–0.66)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Any blood transfusion</td>
<td>11 (3.9%)</td>
<td>27 (9.5%)</td>
<td>0.39* (0.17–0.84)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Percentages are calculated from the Kaplan-Meier curve. TIMI=Thrombolysis in Myocardial Infarction criteria. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria. BARC=Bleeding Academic Research Consortium criteria. *Odds ratio.

Table 3: Results for the primary endpoint at 1 year
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Double therapy (n=297)</th>
<th>Triple therapy (n=284)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined secondary endpoint</td>
<td>31 (11.1%)</td>
<td>50 (17.6%)</td>
<td>0.60 (0.38-0.94)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>7 (2.5%)</td>
<td>18 (6.3%)</td>
<td>0.39 (0.16-0.93)</td>
<td>0.027</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3 (1.1%)</td>
<td>7 (2.5%)</td>
<td>0.43 (0.11-1.66)</td>
<td>0.207</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>4 (1.4%)</td>
<td>11 (3.9%)</td>
<td>0.36 (0.11-1.13)</td>
<td>0.069</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>9 (3.2%)</td>
<td>13 (4.6%)</td>
<td>0.69 (0.29-1.60)</td>
<td>0.382</td>
</tr>
<tr>
<td>STEMI</td>
<td>1 (0.4%)</td>
<td>3 (1.1%)</td>
<td>0.34 (0.04-3.25)</td>
<td>0.325</td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>8 (2.9%)</td>
<td>10 (3.5%)</td>
<td>0.79 (0.31-2.01)</td>
<td>0.625</td>
</tr>
<tr>
<td>Target-vessel revascularisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>20 (7.2%)</td>
<td>19 (6.7%)</td>
<td>1.05 (0.56-1.97)</td>
<td>0.876</td>
</tr>
<tr>
<td>PCI</td>
<td>17 (6.1%)</td>
<td>16 (5.6%)</td>
<td>1.06 (0.54-2.10)</td>
<td>0.869</td>
</tr>
<tr>
<td>CABG</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>1.00 (0.20-4.90)</td>
<td>0.998</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3 (1.1%)</td>
<td>8 (2.8%)</td>
<td>0.37 (0.10-1.40)</td>
<td>0.128</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>2 (0.7%)</td>
<td>8 (2.8%)</td>
<td>0.25 (0.05-1.17)</td>
<td>0.056</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>NA</td>
<td>0.321</td>
</tr>
<tr>
<td>Disabling</td>
<td>2 (0.7%)</td>
<td>2 (0.7%)</td>
<td>0.99 (0.14-6.99)</td>
<td>0.988</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>1 (0.4%)</td>
<td>7 (2.5%)</td>
<td>0.14 (0.02-1.16)</td>
<td>0.034</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>4 (1.4%)</td>
<td>9 (3.2%)</td>
<td>0.44 (0.14-1.44)</td>
<td>0.165</td>
</tr>
<tr>
<td>Definite</td>
<td>1 (0.4%)</td>
<td>3 (1.1%)</td>
<td>0.33 (0.03-3.22)</td>
<td>0.319</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>2 (0.7%)</td>
<td>NA</td>
<td>0.161</td>
</tr>
<tr>
<td>Possible</td>
<td>3 (1.1%)</td>
<td>4 (1.4%)</td>
<td>0.75 (0.17-3.30)</td>
<td>0.708</td>
</tr>
</tbody>
</table>
WOEST Trial limitations

- Only 69% of patients received OAC due to AF

- Most of the patients underwent elective PCI (70–75%)

- The femoral approach was used in 74%, increasing access site bleeding

- The differences between dual and triple therapy for the primary end-point of ‘all bleeding’ were driven by minor bleeding events

- Proton pump inhibitors (PPIs) were not used routinely

- Triple therapy was continued for 12 months (and thus, the increased risk of bleeding is unsurprising)

- The trial population size was too small to meaningfully assess major efficacy outcomes such as stent thrombosis or death