DAPT and NOAC in patient undergoing PCI: a mission impossible?

Loris Roncon
EPIDEMIOLOGY

• Coronary artery disease co-exists in 20-30% of patients in AF

• 8-10% of pts undergoing PCI have AF

• 15–20% of post ACS or electively stented patients are estimated to develop AF and are therefore candidates for anticoagulation
Atrial Fibrillation: OAC vs. DAPT

Stent thrombosis

Coronary stent implantation

Cardiac Events

Cumulative Incidence (%)

Days after Stenting

Oral Anticoagulation

Dual Antiplatelet

ISAR, NEJM 1996

Atrial fibrillation

Cumulative Hazard Rates

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

Dual Antiplatelet

Oral Anticoagulation

ACTIVE-W Lancet 2006

Dual Antiplatelet + Oral Anticoagulation

Loris Roncon
The clinical challenge in patients with atrial fibrillation undergoing PCI

5-10% of patients undergoing PCI have atrial fibrillation

**STROKE**

OAC > DAPT for Stroke prevention

**STENT THROMBOSIS**

DAPT > OAC for Stent Thrombosis prevention

TRIPLE THERAPY

BLEEDING

Triple therapy with DAPT and NOACs at least doubles the risk of major bleeding after an ACS. As a rule of thumb, adding a SAPT drug to (any type of) oral anticoagulation increases the major bleeding risk by 60–80%; adding dual antiplatelet drugs increases major bleeding with at least 130% over anticoagulation only.

*Updated EHRA practical guide for use of the non-VKA oral anticoagulants 2015*
Impact of bleeding on mortality in patients undergoing PCI

- 30 day major bleeding after PCI is a strong independent risk factor for 1-year mortality with a 3-fold hazard, higher than the ~2.5 hazard estimate for post-procedural MI

Ndrepepa et al. JACC 2008;
Pocock et al. Circulation 2010
WOEST: reduced bleeding risk and no increase in thrombosis with double vs triple antithrombotic therapy

WOEST was a small trial in patients with a long-term indication for OAC and an indication for PCI. AF was not a prerequisite; however, 69% of patients in both the double therapy and triple therapy treatment groups were using OACs for AF/atrial flutter

OAC + clopidogrel associated with significant reduction in major bleeding and no increase in thrombotic events vs triple therapy with OAC + clopidogrel + ASA

573 patients receiving OAC and undergoing PCI in open-label, randomized WOEST trial
ST = stent thrombosis; TIMI = thrombolysis in myocardial infarction bleeding criteria
Antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
</tr>
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<td>IIa</td>
</tr>
<tr>
<td>Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.</td>
<td>IIb</td>
</tr>
<tr>
<td>The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended.</td>
<td>III</td>
</tr>
</tbody>
</table>

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2014 ESC/EACTS Guidelines on myocardial revascularization
NVAF and PCI: a broad spectrum of options

- ASA alone
- Clopidogrel alone
- Ticagrelor alone
- Warfarin alone
- NOAC alone

- ASA + warfarin
- Clopidogrel + warfarin
- Prasugrel + warfarin
- Ticagrelor + warfarin
- ASA + NOAC
- Clopidogrel + NOAC (low dose)
- Clopidogrel + NOAC (high dose)
- Prasugrel + NOAC
- Ticagrelor + NOAC

- ASA + clopidogrel + warfarin
- ASA + prasugrel + warfarin
- ASA + ticagrelor + warfarin
- ASA + clopidogrel + NOAC (low dose)
- ASA + clopidogrel + NOAC (high dose)
- ASA + prasugrel + NOAC
- ASA + ticagrelor + NOAC

NOAC = novel oral anticoagulant
Triple Therapy With Aspirin, Prasugrel, and Vitamin K Antagonists in Patients With Drug-Eluting Stent Implantation and an Indication for Oral Anticoagulation

Triple therapy of VKA + aspirin + clopidogrel/prasugrel after PCI

HR 4.6 (95% CI 1.9-11.4; p<0.001)

HR 1.4 (95% CI 0.3-6.1; p= 0.61)

### 2014 ESC/EACTS Guidelines on myocardial revascularization

**Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation**

<table>
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</table>
Percentages refer use of antiplatelet during the study period

<table>
<thead>
<tr>
<th></th>
<th>RE-LY DABIGATRAN</th>
<th>ROCKET-AF RIVAROXABAN</th>
<th>ARISTOTLE APIXABAN</th>
<th>ENGAGE EDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of ASA alone</td>
<td>32 %</td>
<td>37 %</td>
<td>24 %</td>
<td>29 %</td>
</tr>
<tr>
<td>Concomitant use of Clopidogrel alone</td>
<td>2 %</td>
<td>&lt; 2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Concomitant use of DAPT</td>
<td>5 %</td>
<td>EXCLUDED</td>
<td>EXCLUDED</td>
<td>EXCLUDED</td>
</tr>
</tbody>
</table>

**NOACS in association with DAPT**

- In all NOACS trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) patients were excluded from enrollment if receiving new P2Y1
- And conversely, AF patients requiring OAC were systematically excluded from recent ACS trials.
- Some data are available in non AF patients
Addition of antiplatelet agents to anticoagulant therapy increases the risk of bleeding

Outcomes from RE-LY®:

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Antiplatelet therapy</th>
<th>None (n=3478)</th>
<th>Single (n=2312)</th>
<th>Dual (n=232)</th>
<th>None (n=3613)</th>
<th>Single (n=2251)</th>
<th>Dual (n=212)</th>
<th>None (n=3510)</th>
<th>Single (n=2288)</th>
<th>Dual (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.8</td>
<td>4.6</td>
<td>6.3</td>
<td>2.6</td>
<td>4.3</td>
<td>5.5</td>
<td>2.2</td>
<td>3.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Major bleeding (%/year)

Triple therapy is associated with the greatest increase in bleeding risk both with dabigatran and with warfarin, but the risk is not higher with dabigatran

Benefits of dabigatran vs warfarin are consistent irrespective of concomitant antiplatelet use

SE = systemic embolism
RE-DEEM
European Heart Journal doi:10.1093/eurheartj/ehr113

- Dabigatan vs. placebo in patients with ACS on DAPT – phase II study
- Dose ranging from 50, 75, 110 and 150mg bd
APPRAISE-2

- Apixaban 5mg bd when added following ACS and DAPT
- Stopped early due to increase major bleed with no counterbalance in reduction of ischaemic events
**ATLAS-TIMI 51 Study Design**

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

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

PLACEBO
- N=5,176
- ASA + Thieno, n=4,821
- ASA, n=355

RIVAROXABAN
- 2.5 mg BID
  - n=5,174
  - ASA + Thieno, n=4,825
  - ASA, n=349

RIVAROXABAN
- 5.0 mg BID
  - N=5,176
  - ASA + Thieno, n=4,827
  - ASA, n=349

**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**

EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine

CV Death / MI / Stroke
Placebo
Rivaroxaban 2.5 mg BID
NNT = 71

Cardiovascular Death
Placebo
Rivaroxaban 2.5 mg BID
NNT = 59

All Cause Death
Placebo
Rivaroxaban 2.5 mg BID
NNT = 56

Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban 2.5 mg BID</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major bleeding not associated with CABG</td>
<td>65 (1.8)</td>
<td>3.46 (2.08–5.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI minor bleeding</td>
<td>32 (0.9)</td>
<td>1.62 (0.92–2.82)</td>
<td>0.09</td>
</tr>
<tr>
<td>TIMI bleeding requiring medical attention</td>
<td>492 (12.9)</td>
<td>1.79 (1.55–2.07)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ad esempio, quale beneficio (o rischio) aggiuntivo possiamo aspettarci dal rivaroxaban nei pazienti trattati con prasugrel o ticagrelor o come dovremo comportarci nel paziente che, dimesso dopo una SCA con una bassa dose di rivaroxaban e la duplice antiaggregazione, sviluppa una FA?
Review

New-onset atrial fibrillation after recent coronary stenting: Warfarin or non-vitamin K-antagonist oral anticoagulants to be added to aspirin and clopidogrel? A viewpoint

Andrea Rubboli a,*, Stefan Agewall b, Kurt Huber c, Gregory Y.H. Lip d
Viewpoint: a proposal for a simple algorithm for managing oral anticoagulation and antiplatelet therapy in patients with non-valvular atrial fibrillation and coronary stents

Steg PG, Bhatt DL. Eur Heart J Acute Cardiovasc Care 2015;
2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

NSTE-ACS patients with non-valvular atrial fibrillation

Management strategy

PCI

Medically managed / CABG

Bleeding risk

Low to intermediate (e.g. HAS-BLED = 0–2)

High (e.g. HAS-BLED ≥3)

Time from PCI/ACS

0

4 weeks

6 months

12 months

Lifelong

Oral anticoagulation (VKA or NOACs)

Aspirin 75–100 mg daily

Clopidogrel 75 mg daily

Triple therapy

Dual therapy

Triple or dual therapy

Dual therapy

Monotherapy

a

b

c

O

A

C

O

A

C

O

A or C

O

C or A

O

C or A

O

C or A

O

O

O

O
Patient with atrial fibrillation and coronary artery disease

Figure 6 Acute management of revascularization or ACS in AF patients treated with NOAC. See text for further discussion.
Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS

**Figure 7** Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.
RE-DUAL PCI:
the largest ongoing study of an OAC in this setting

Phase IIIb, prospective, randomized, open-label, blinded endpoint (PROBE) active-comparator study

Worldwide event-driven trial; 2840 patients per treatment arm (total 8520 patients)

RE-DUAL PCI™ will investigate two new approaches to improving care for patients with NVAF undergoing PCI

Two new regimens with dabigatran: 150 or 110 mg BID plus single antiplatelet (P2Y12 inhibitor)

‘Enhanced’ standard of care: VKA plus dual antiplatelets (but with earlier discontinuation of ASA)

*Patients aged ≥80 years outside of the USA will be assigned to 110 mg dabigatran etexilate or warfarin in a 1:1 ratio
VKA = Vitamin K antagonist
Adapted from Cannon C. AHA 2013 and Boehringer Ingelheim data on file
RE-DUAL PCI design

Screening → n=2840 patients per arm

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

1° EP

Dual primary endpoints of efficacy and safety
- Time to death or first thrombotic event (death, MI, stroke/SE)
- Time to first ISTH major bleeding event

ISTH = International Society on Thrombosis and Haemostasis
XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI

- **2100 patients with NVAF**
- **No prior stroke/TIA**
- **PCI with stent placement**

**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.
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)

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

**Warfarin**
- 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

Loris Roncon
**EVOLVE-AF Trial**

**Figure 1. Schematic presentation of the study design:**

- **PROBE design:** open label edoxaban vs. VKA
- Blinded adjudication of endpoints by independent CEC

**Edoxaban + P2Y₁₂ antagonist**
- Edoxaban 60 mg once daily with dose reduced to 30 mg for factors requiring dose adjustment
- P2Y₁₂ antagonist for 1, 3, 6 or 12 months as per individual patient's need based on regional guidelines (Investigator to declare the duration of P2Y12 therapy at randomization)

**VKA + P2Y₁₂ antagonist + Aspirin**
- VKA dose adjusted to maintain INR: 2-3
- P2Y₁₂ antagonist 1, 3, 6 or 12 months as per individual patient's need and based on regional guidelines (Investigator to declare the duration of P2Y12 therapy at randomization)
- Aspirin for 0, 1, 3, 6 or 12 months (Investigator to declare the duration aspirin therapy at randomization)

**Stratify before randomization:**
- ACS or elective PCI
- BMS or DES
- Need for edoxaban dose reduction: No vs. Yes (CrCl <50 ml/min or body weight <60 or P-gp inhibitors)

**Patients with AF following Successful PCI with stent placement**

4-72 hrs After sheath removal

12 months: end of treatment

**Primary endpoint:** Major or CR non-major bleed event
**Primary comparison:** All edoxaban-treated subjects vs. all VKA-treated subjects (12 month follow-up)
Nei pazienti scoagulati sottoposti ad impianto di DES quale dei seguenti schemi di terapia antitrombotica adottate?

- TAO + DAPT per 3/6 mesi quindi TAO + ASA o Clopidogrel: 64,6%
- TAO + singolo antiaggregante: 7,1%
- DAPT per alcuni mesi (in relazione alla presentazione clinica e/o al tipo di stent utilizzato), successivamente TAO/NAO + singolo antiaggregante: 14,1%
- NAO + DAPT per 12 mesi: 1,0%
- TAO + DAPT per 12 mesi: 5,1%
- NAO + DAPT per 3/6 mesi quindi NAO + ASA o Clopidogrel: 8,1%
Conclusions

- AFib is present in 5–10% of the patients with ACS and increases with age, presence of heart failure and comorbidity

- PCI should be performed via a radial approach with use of additional parenteral anticoagulation, regardless of the timing of the last dose of oral anticoagulant

- The use of ticagrelor and prasugrel is not recommended

- New-generation DES are preferred over BMS if bleeding risk is low (HAS-BLED ≤ 2)

- In patients at low bleeding risk (HAS-BLED ≤ 2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.

- In patients at high bleeding risk (HAS-BLED ≥ 3), triple therapy of (N)OAC and ASA and clopidogrel should be considered for a duration of one month followed by (N)OAC and aspirin or clopidogrel irrespective of stent type

- Use of lower tested dose in the case of NOACs (dabigatran 100 mg b.i.d.; rivaroxaban 15 mg once daily, apixaban 2.5 mg b.i.d.; etc.).
Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel¹*, Peter Verhamme², Marco Alings³, Matthias Antz⁴, Hans-Christoph Diener⁵, Werner Hacke⁶, Jonas Oldgren⁷, Peter Sinnaeve², A. John Camm⁸, and Paulus Kirchhof⁹,¹⁰