ATRIAL FIBRILLATION and CORONARY ARTERY DISEASE

The need for concomitant therapy with antiplatelet agents

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EHRA Scientific Document Committee member
Conflict of Interest

• Consultant for Bayer Serbia
• Speaker fees from Bayer
• IIR grant from Pfizer
Thrombosis is responsible for 1 in 4 deaths worldwide.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Ischemic Heart Disease*</th>
<th>Ischemic Stroke*</th>
<th>AF*</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>59.5 f (2010)</td>
<td></td>
</tr>
<tr>
<td>YLDs</td>
<td>5.8 (2013)</td>
<td>2.7 (2013)</td>
<td>0.9 (2013)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Estimates from the Global Burden of Disease project.

AF: Atrial Fibrillation; VTE: Venous Thromboembolism; YLD: Years Lived with Disability; DALY: Disability-adjusted life year.

THE SPECTRUM OF ARTERIAL THROMBOTIC DISEASE


MI: Myocardial Infarction; CAD: Coronary Artery Disease; PAD: Peripheral Artery Disease; CBVD: Cerebral Vascular Disease.
AF and CAD commonly occur together owing to the strong association of both conditions with aging and CV risk factors.

1 Billion individuals in Europe and US

20 Million with AF (≥2% of the general population)\(^1\)\(^-\)\(^3\)

16 Million AF patients need long-term OAC (\(~80\%)\(^2\)\(^,\)\(^3\)

4.8 Million AF patients who need long-term OAC also have CAD\(^2\)\(^,\)\(^3\)

1-2 Million AF + CAD patients may need revascularization (20-25%)\(^4\)\(^,\)\(^5\)

Antithrombotic therapy for AF and PCI

5% - 25% of patients with ACS undergoing PCI have concomitant AF\(^1\)

AF + PCI = AF and PCI

- Anticoagulant therapy (OAC)
  - Low shear stress thrombosis in the LA
  - OAC superior to APLT

- Antiplatelet therapy (APLT)
  - High shear stress arterial thrombosis
  - DAPT superior to ASA alone

- Triple therapy: OAC and APLT
  - High bleeding risk

Danish Registry: Risk of Bleeding With Antithrombotic Therapy

Study period: 2000 – 2005
N=40,812 pts admitted with **first-time MI**
Mean follow-up: 16 months
Highest bleeding rate: VKA +DAPT
4-fold higher risk than with aspirin alone

Study period: Jan 1997 - Dec 2006
N=82,854 pts admitted for **first-time AF**
Mean follow-up: 3.3 years
Overall bleeding rate: 11.4%
~4-fold higher risk than warfarin alone

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**Danish Registry Study of Patients With MI**

**Risk of Bleeding With Antithrombotic Therapy**

- **Aspirin alone**: 1
- **Clopidogrel alone**: 1.33
- **VKA**: 1.23
- **Aspirin + Clopidogrel**: 1.47
- **Aspirin + VKA**: 1.84
- **Clopidogrel + VKA**: 3.52
- **Triple therapy**: 4.05

**Hazard Ratio**

**95% CI Reference**

- 1.11, 1.59
- 0.94, 1.61
- 1.28, 1.69
- 1.51, 2.23
- 2.42, 5.11
- 3.08, 5.33

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**Danish Registry Study of Patients With AF**

**Risk of Bleeding With Antithrombotic Therapy**

- **Warfarin monotherapy**: 1
- **Aspirin monotherapy**: 0.33
- **Clopidogrel monotherapy**: 1.06
- **Aspirin + clopidogrel**: 1.66
- **Warfarin + aspirin**: 1.83
- **Warfarin + clopidogrel**: 3.08
- **Triple therapy**: 3.70

**Hazard Ratio**

**95% CI Reference**

- 0.88, 0.98
- 0.87, 1.29
- 1.34, 2.04
- 1.72, 1.96
- 2.32, 3.91
- 2.89, 4.75

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N = 82,854 patients who survived hospitalization had ≥ 1 prescription at discharge

Case:

A 68-y old male patient at discharge post anterior STEMI with PCI and DES implantation in proximal LAD

- **Paroxysmal AF** for 3y (4-5 AF episodes per year), intermittent warfarin use (TTR 49%)
- **Hypertension** in the last 10 years
- **Mild ischemic stroke** 2 years ago

- TTE: LVEF 60%, MR 1+, LA 45mm (28mL)

- Beta blocker, ARB, Thiazid diuretic, Statin, PPI
- **Aspirin 100mg daily, Ticagrelor 90mg BID, ?**

\( \text{CHA}_2\text{DS}_2\text{-VASc} = 5 \)
\( \text{HAS-BLED} = 3 \)
Antithrombotic therapy for AF and PCI

- **Aspirin**
- **P2Y\(_{12}\)**
- **Warfarin**
- **NOAC**

**Single Therapy**
- Aspirin + P2Y\(_{12}\)
- Warfarin
- NOAC

**DAPT**
- Aspirin + P2Y\(_{12}\)
- clopidogrel (or ticagrelor or prasugrel)

**Double therapy**
- P2Y\(_{12}\) + Warfarin
- P2Y\(_{12}\) + NOAC

**Triple therapy**
- Aspirin + P2Y\(_{12}\) + Warfarin
- Aspirin + P2Y\(_{12}\) + NOAC

Increasing risk of bleeding
Increasing risk of thrombosis

In patients with stents, P2Y\(_{12}\) inhibition has a key role in the prevention of TE complications.
Danish Registry: Use of OAC in combination with antiplatelet(s) in AF


Study period: 2011-2016
N=2946; AF pts who survived 30 d after discharge from MI and/or PCI
Danish Registry: NOAC or VKA with antiplatelets in patients with AF and MI or PCI


- Patients admitted with a MI and/or undergoing a PCI between 2011-2016
- N=2,593; 12-month f-up

Group 1: VKA + SAPT
N=792

Group 2: NOAC + SAPT
N=452

Group 3: VKA + DAPT
N=880

Group 4: NOAC + DAPT
N=469
WOEST: Study Design

Open label, multicenter RCT

Patients needing OAC after PCI with stent placement

N=573

R 1:1

≤4 hrs post PCI

Triple therapy (OAC + Clopidogrel + ASA)

N=284

APLT treatment duration
- BMS for stable CAD: ≥1 month up to 1 y
- DES or ACS: clopidogrel for ≥1 y

N=279

Dual therapy (OAC + Clopidogrel) No Aspirin

Primary outcome: combination of TIMI and GUSTO minor/major bleeding at 30 days and 1 y

Secondary outcome: Major Adverse Cardiac Event (MACE) – Death, MI, Stroke, Revascularisation, Stent thrombosis

Patient characteristics | Double therapy % (n) | Triple therapy % (n)
--- | --- | ---
AF | 69% (164/236) | 69% (162/234)
ACS | 25% (62) | 30% (86)
LVEF<30% | 21% (40/190) | 18% (37/206)
Mechanical valve | 10% (24/236) | 11% (25/234)

Double therapy
• Significantly lowered risk of bleeding
• No increased risk of thrombotic events

Limitations
Small study
23% power to detect differences in efficacy outcomes

WOEST Trial: Omission of Aspirin Reduces Bleeding

WOEST Trial: Less Bleeding With Dual Therapy in Patients Undergoing PCI
The efficacy and safety of NOACs and concomitant aspirin therapy in AF: Meta-analyses of the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE-AF trials

N=21,722/71,681 patients (30%)

<table>
<thead>
<tr>
<th>OAC+APLT vs. OAC alone</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboembolic risk</strong></td>
<td></td>
</tr>
<tr>
<td>NOAC + APLT vs. NOAC alone</td>
<td>1.16 (1.05-1.29)</td>
</tr>
<tr>
<td>Warfarin + APLT vs. Warfarin alone</td>
<td>1.28 (1.14-1.44)</td>
</tr>
<tr>
<td>Total</td>
<td>1.21 (1.12-1.31)</td>
</tr>
<tr>
<td><strong>Bleeding risk</strong></td>
<td></td>
</tr>
<tr>
<td>NOAC + APLT vs. NOAC alone</td>
<td>1.33 (1.25-1.42)</td>
</tr>
<tr>
<td>Warfarin + APLT vs. Warfarin alone</td>
<td>1.28 (1.19-1.37)</td>
</tr>
<tr>
<td>Total</td>
<td>1.31 (1.25-1.37)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>NOAC+APLT vs. Warfarin+APLT</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.93 (0.73-1.18)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0.85 (0.76-0.93)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.83 (0.69-1.01)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.38 (0.26-0.56)</td>
</tr>
<tr>
<td>MI</td>
<td>1.16 (0.97-1.39)</td>
</tr>
</tbody>
</table>
**Primary outcome:** Clinically relevant bleeding (composite of TIMI major or minor, or bleeding requiring medical attention)

**Secondary outcome:** MACE (composite of CV Death, MI or Stroke)
Both Riva arms significantly reduced bleeding, with no significant increase in thrombotic risks.
All Cause Hospitalization for an Adverse Event

- **Riva + P2Y₁₂ v. VKA + DAPT**
  - HR=0.77 (95% CI: 0.65-0.92)
  - p=0.005
  - ARR=7.4
  - NNT=14

- **VKA + DAPT**
  - 31.2%

- **Riva + DAPT**
  - 34.1%

**Hospitalization Related to Cardiovascular or Bleeding Event**

- **Cardiovascular events**
  - **Riva + P2Y₁₂ v. VKA + DAPT**
    - HR=0.68 (95% CI: 0.54-0.85)
    - P<0.001
    - ARR=8.1; NNT=13

- **Bleeding events**
  - **Riva + DAPT v. VKA + DAPT**
    - HR=0.73 (95% CI: 0.58-0.91)
    - p=0.005
    - ARR=8.1; NNT=13

RE-DUAL PCI: Study Design

![Study Design Diagram](image)

**Patients with AF undergoing PCI with stenting**

N=2725

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

6-month minimum treatment duration with visits every 3 months for the first year, then visits and telephone contact alternating every 3 months and a 1-month post-treatment visit

**Mean duration of follow-up:** ~14 months

*CStudy drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable). PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016*

Cannon C et al. NEJM 2017; doi:10.1056/NEJMoa1708454
Both dual therapy arms significantly reduced bleeding.
No significant increase in thrombotic risks with dual therapy

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg Dual Therapy (N = 981), %</th>
<th>Warfarin triple therapy (N = 981), %</th>
<th>Dabigatran 110 mg Dual Therapy vs Warfarin Triple Therapy</th>
<th>Dabigatran 150 mg Dual Therapy vs Warfarin Triple Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>DTE or unplanned revascularization</td>
<td>15.2 (1.13) (0.90, 1.43)</td>
<td>13.4 (1.12) (0.76, 1.65)</td>
<td>.30</td>
<td>.89 (0.60, 1.19)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>5.6 (1.12) (0.76, 1.65)</td>
<td>4.9 (1.30) (0.63, 2.67)</td>
<td>.56</td>
<td>.83 (0.51, 1.34)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.7 (1.09) (0.79, 1.51)</td>
<td>1.3 (1.09) (0.42, 2.83)</td>
<td>.48</td>
<td>.83 (0.51, 1.34)</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>7.7 (1.09) (0.79, 1.51)</td>
<td>7.0 (1.30) (0.63, 2.67)</td>
<td>.61</td>
<td>.83 (0.65, 1.41)</td>
</tr>
<tr>
<td>MI</td>
<td>4.5 (1.51) (0.94, 2.41)</td>
<td>3.0 (1.86) (0.79, 4.40)</td>
<td>.09</td>
<td>.99 (0.35, 2.81)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.5 (1.86) (0.79, 4.40)</td>
<td>0.8</td>
<td>.15</td>
<td>.98 (0.35, 2.81)</td>
</tr>
</tbody>
</table>

Cannon C et al. NEJM 2017; doi:10.1056/NEJMoa1708454
# ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH RECENT ACS / CAD and AF

<table>
<thead>
<tr>
<th>RCT</th>
<th>Cohort</th>
<th>Treatment arms</th>
<th>Primary outcome</th>
<th>Stent thrombosis</th>
<th>Antiplatelet agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIONEER AF-PCI</td>
<td>N=2124</td>
<td>•Riva 15mg OD+P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>16.8%</td>
<td>0.8%</td>
<td>4% Ticagrelor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Riva 2.5mg bid+DAPT</td>
<td>18.0%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>•VKA+DAPT</td>
<td>26.7%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>N=2725</td>
<td>•Dabi 150mg bid+P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>20.2%</td>
<td>0.9%</td>
<td>12% Ticagrelor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Dabi 110mg bid+P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>15.4%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>•VKA+DAPT</td>
<td>25.7% / 26.9%</td>
<td>0.9% / 0.8%</td>
<td></td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>Ongoing</td>
<td>•Apix  5mg bid+P2Y&lt;sub&gt;12&lt;/sub&gt;+ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=4600</td>
<td>•VKA+P2Y&lt;sub&gt;12&lt;/sub&gt; ± ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENTRUST-AF PCI</td>
<td>Ongoing</td>
<td>•Edoxa 60mg OD+P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
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<tr>
<td></td>
<td></td>
<td>•VKA+DAPT</td>
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</tbody>
</table>

OD: Once daily; DAPT: Dual antiplatelet therapy; ASA: Acetylsalicylic acid; MACE: Major Adverse Cardiovascular Event; CV: Cardiovascular; MI: Myocardial infarction; CRNM: Clinically Relevant Non-Major; TE: Thromboembolic; SE: Systemic embolic event.

PIONEER AF-PCI: N Engl J Med 2016; 175:3423; RE-DUAL PCI:
1. Assess stroke risk (CHA₂DS₂-VASc)
2. Assess bleeding risk (HAS-BLED)
3. Consider clinical setting
4. Select antithrombotic therapy

Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.
2015 ESC NSTEMI Guidelines
Eur Heart J 2016; 17:267.
Management during STEMI:

- **Triage for primary PCI** (OAC is a relative contraindication for fibrinolysis).
- **Use additional parenteral anticoagulation** as usual.
- Avoid GP IIb/IIIa inhibitors.
- Load with aspirin as usual.
- Among P2Y$_{12}$ inhibitors preferably use clopidogrel (600mg per os).
- Do not stop OAC if possible.
- Use gastric protection with PPIs.

Maintenance after STEMI:

- **Triple therapy at least 6 months post primary PCI** for most patients, followed by dual therapy (OAC+ASA or a P2Y$_{12}$ inhibitor) for another 6 months and then, after 1 year, OAC only.
- **In cases of very high bleeding risk consider triple therapy for 1 month**, then OAC+ASA or clopidogrel up to 1 year, and then OAC only.
- If OAC was a NOAC, use the lowest effective NOAC dose for SPAF during the combination therapy.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAPT : ASA + Ticagrelor or Prasugrel (or clopidogrel) for 12 mo after PCI</strong></td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A PPI in combination with DAPT in patients at risk of GI bleeding</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with an indication for OAC, triple therapy (OAC + DAPT)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients at high risk of severe bleeding, consider discontinuation of P2Y&lt;sub&gt;12&lt;/sub&gt; after 6 mo</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>In STEMI with stent implantation and an indication for OAC, triple therapy for 1-6 mo (according to the risk of recurrent coronary event/bleeding)</strong></td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>DAPT for 12 mo in STEMI without PCI if the risk of bleeding is not very high</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Consider Ticagrelor 60mg bid + ASA for &gt;12 mo to 3 y in STEMI with high ischemic risk</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>If low bleeding risk, ASA+Clopidogrel+Riva 2.5mg bid may be considered</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>Ticagrelor or prasugrel in triple therapy (with ASA+OAC) is not recommended</strong></td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Conclusions

• Patients at risk of arterial thrombotic events often require combined antithrombotic therapy.

• The risk of bleeding is 2- to 3-fold greater with OAC+DAPT.

• The use of NOACs with concomitant P2Y$_{12}$ is associated with lower risk of bleeding in comparison with conventional triple therapy of VKA+DAPT.

• Recent data suggest that aspirin may be omitted or discontinued early post an acute event, but more data are needed to inform optimal management of these patients.