The patient with atrial fibrillation who needs PCI.
The anticoagulant/antiplatelet conundrum.

Kostadin Kichukov, MD, PhD
City Clinic – Sofia
Department cardiology and angiology
Who needs anticoagulation for AF?
Almost everyone!

• Based on the current guidelines of the ESC the thromboembolic risk stratification is widely based on the the scoring systems like CHADS\textsubscript{2} and more recently the CHA\textsubscript{2}DS\textsubscript{2}-VASc Score.

• If we simply apply the CHADS\textsubscript{2} score almost 70-80% of the AF patients will be eligible for oral anticoagulation (OAC). If you apply the CHA\textsubscript{2}DS\textsubscript{2}-VASc Score – the number could increase to almost 94%.

• On the other hand 20-30% of AF patients have coronary artery disease (CAD) and about 10% of patients with acute coronary syndromes (ACS) have AF.

We are facing a conundrum! We have to much variables to balance between.

- **AF + OAC** – Embolism vs bleeding?
- **AF** – OAC vs novel OAC?
- **PCI + DAPT** duration – Stent thrombosis vs bleeding?
- **PCI** – standard vs novel antiplatelets?
Where to start from?

- **First – indication for PCI - unmodifiable**
  - Elective
  - ACS
    - STEMI and PPCi;
    - NSTE-ACS – mid, longterm
  - Type of stent - modifiable

- **Bleeding risk**
  - HAS-BLED Score system: 3+ - High risk

- Atrial Fibrillation (Management of) 2010 and Focused Update (2012) ESC Clinical Practice Guidelines
What the real situation is?

• On one hand in ACS patients DAPT should be continued for 12 months.

• Real life patients are usually much more complex. These AF patients are usually elderly with a high prevalence of diabetes and unfavorable coronary anatomy (multivessel disease; long, calcified small vessel lesions). Ideally, single focal lesions would be found in large vessels, where only a conventional stent would be implanted.

• Guideline recommendations have clear arguments for their strategies, i.e. that “DES should be avoided” and “DES should be limited to clinical and anatomical situations with high risk of restenosis”. These 2 contrasting positions must be discussed in each individual case between the clinical and interventional cardiologists, balancing the pros and cons of both strategies.
What to mind during and post PCI?

• First choice - radial approach:
  – The femoral approach is an independent predictor of access site complications in warfarin treated patients (a hazard ratio of 9.9).

• In PPCI for STEMI:
  – Mechanical thrombus removal is encouraged.
  – GPIs or bivalirudin would not be considered if the INR is >2, except in a ‘bail-out’ option.

• Try to avoid bridging with Heparin.

• DES should be limited to only situations with clear benefit.

• In NSTEMI - Uninterrupted OAC strategy is recommended

• **Target INR – 2.0-2.5**
## What the guidelines actually say?

<table>
<thead>
<tr>
<th>Haemorrhagic risk</th>
<th>Clinical setting</th>
<th>Stent implanted</th>
<th>Anticoagulation regimen</th>
</tr>
</thead>
</table>
| Low or intermediate (e.g. HAS-BLED score 0–2) | Elective         | Bare-metal      | 1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day  
Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day  
(or aspirin 100 mg/day)  
Lifelong: VKA (INR 2.0–3.0) alone |
| Elective                               | Drug-eluting     |                 | 3-6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day  
Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day  
(or aspirin 100 mg/day)  
Lifelong: VKA (INR 2.0–3.0) alone |
| ACS                                    | Bare-metal/drug-eluting |            | 6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day  
Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day  
(or aspirin 100 mg/day)  
Lifelong: VKA (INR 2.0–3.0) alone |
| High (e.g. HAS-BLED score ≥3)          | Elective         | Bare-metal      | 2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day  
Lifelong: VKA (INR 2.0–3.0) alone |
| ACS                                    | Bare-metal      |                 | 4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day  
Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day  
(or aspirin 100 mg/day)  
Lifelong: VKA (INR 2.0–3.0) alone |
Practically – an easy algorithm

AF and stenting with moderate/high stroke risk (CHA$_2$DS$_2$-VASc$\geq$1)

Hemorrhagic risk (HAS-BLED score)

Low or intermediate (HAS-BLED$=0-3$)

- BMS
  - 1 month: TT+gastric protection
  - 1-12 months: OAC+1 antplatelet
  - Lifelong: OAC alone

- DES
  - 6 months: TT+gastric protection
  - 6-12 months: OAC+1 antplatelet
  - Lifelong:
    - OAC alone
    - OAC+1 antplatelet in high TR

High (HAS-BLED$>3$)

- BMS
  - 1 month: TT+gastric protection
  - 1-12 months:
    - OAC alone
    - OAC+1 antplatelet in high TR
  - Lifelong: OAC alone

- DES
  - 3 months: TT+gastric protection
  - 3-12 months: OAC+1 antplatelet
  - Lifelong:
    - OAC alone
    - OAC+1 antplatelet in high TR

Things could be easier. Try WOEST.

• WOEST - Tests the hypothesis that in patients on OAC undergoing PCI, clopidogrel alone is superior to the combination aspirin and clopidogrel with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (BE, NL).
WOEST

Study Design

1:1 Randomisation:

Dual therapy group:
- OAC + 75mg Clopidogrel qd

Triple therapy group:
- OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

1 month minimum after BMS
1 year after DES

Follow up: 1 year

Primary Endpoint: The occurrence of all bleeding events (TIMI criteria)

Secondary Endpoints:
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
Primary Endpoint: Total number of bleeding events

- Triple therapy group: 44.9%
- Double therapy group: 19.5%

p < 0.001
HR = 0.36, 95% CI [0.26-0.50]
Locations of TIMI bleeding: Worst bleeding per patient

<table>
<thead>
<tr>
<th>Location</th>
<th>Double therapy group</th>
<th>Triple therapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-Cranial</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Access site</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>GI</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>48</td>
</tr>
</tbody>
</table>
WOEST

Secondary Endpoint

<table>
<thead>
<tr>
<th>Event</th>
<th>Double Therapy Group</th>
<th>p-value</th>
<th>Triple Therapy Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.6</td>
<td>0.027</td>
<td>4.7</td>
</tr>
<tr>
<td>MI</td>
<td>3.3</td>
<td>0.382</td>
<td>6.4</td>
</tr>
<tr>
<td>TVR</td>
<td>7.3</td>
<td>0.876</td>
<td>6.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1</td>
<td>0.128</td>
<td>2.9</td>
</tr>
<tr>
<td>ST</td>
<td>1.5</td>
<td>0.165</td>
<td>3.2</td>
</tr>
</tbody>
</table>
WOEST - Conclusions

• First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting.

• Primary endpoint was met: as expected, OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way.

• Secondary endpoint was met: with dual therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death.

• Less all-cause mortality with dual therapy.
What about novel anticoagulant (NOAC) regimens in AF and PCI?

• Patients taking the NOACs may present with an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). Concomitant use of antiplatelet therapy with the NOACs significantly increases bleeding risk, as is the case with combining any OAC with antiplatelet therapy. In AF patients at risk of stroke, and irrespective of HAS-BLED score, OAC still confers benefit (reduced mortality and major adverse cardiac events) but with more bleeds.

• In the absence of robust data, in AF patients with an ACS or PCI/stenting, recommendations based on expert consensus on the management of such patients should
What about NOAC regimens in AF and PCI? (2)

• Thus, a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination OAC plus single antiplatelet drug and, after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably a NOAC.

• Notably, the only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited.
Dabigatran and ACS
The **RE-DEEM** Phase II Trial

- 1878 pts at very high risk randomized
- Up to 14 days of STEMI or NSTEMI
- All on dual antiplatelet therapy
- 6 arms – placebo/DGT 50/75/110/150 mg;
- At week 28 – still 79.6% were taking DAPT
Dabigatran and ACS. The **RE-DEEM** Phase II Trial

**Figure 1** Study design (adaptive dose-escalation) and patient flow.
Figure 2 Kaplan–Meier curve depicting the primary endpoint, i.e. the composite of major and clinically relevant minor bleeding. Compared with placebo, primary outcomes differed significantly ($P < 0.001$) for the 110 and 150 mg dabigatran doses using Cox proportional hazards regression models. Number of subjects at risk are given below the x-axis.
Dabigatran and ACS - The RE-DEEM Phase II Trial

Conclusion

• 6 months treatment with Dabigatran 50-150 mg in post-MI pts, receiving DAPT was associated with two to four times dose-related increase in bleeding.

• The study had no power to detect the net clinical benefit.
What about NOAC regimens in AF and PCI? (3)

- A patient taking Dabigatran may present with an ACS and, given the non-significant but small numerical increase in MI events with dabigatran compared with warfarin, the concerned clinician may consider the use of a VKA or an alternative NOAC (e.g. rivaroxaban or apixaban). There is little evidence to support this, as the relative effects of dabigatran vs. warfarin on myocardial ischaemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.
Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Table 2. Risk of MI/ACS Across 7 Studies, Including Original RE-LY Results

<table>
<thead>
<tr>
<th>Measure of Association</th>
<th>Method</th>
<th>Association (95% CI)</th>
<th>P Value for Effect</th>
<th>Degree of Heterogeneity ($I^2$)</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>M-H</td>
<td>1.33 (1.03 to 1.71)</td>
<td>.03</td>
<td>0% for all</td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>Peto</td>
<td>1.29 (1.03 to 1.62)</td>
<td>.03</td>
<td></td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>1.30 (1.02 to 1.65)</td>
<td>.04</td>
<td></td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>RE</td>
<td>1.32 (1.03 to 1.70)</td>
<td>.03</td>
<td></td>
<td>.80</td>
</tr>
<tr>
<td>Relative risk</td>
<td>M-H</td>
<td>1.33 (1.03 to 1.70)</td>
<td>.03</td>
<td>0% for all</td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>1.31 (1.02 to 1.69)</td>
<td>.03</td>
<td></td>
<td>.80</td>
</tr>
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<td></td>
<td>RE</td>
<td>1.32 (1.02 to 1.69)</td>
<td>.03</td>
<td></td>
<td>.80</td>
</tr>
<tr>
<td>Risk difference</td>
<td>M-H</td>
<td>0.27% (0.04% to 0.50%)</td>
<td>.02</td>
<td>0% for all</td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>0.14% (-0.03% to 0.31%)</td>
<td>.10</td>
<td></td>
<td>.40</td>
</tr>
<tr>
<td></td>
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<td>0.14% (-0.03% to 0.32%)</td>
<td>.10</td>
<td></td>
<td>.40</td>
</tr>
</tbody>
</table>
What about NOAC regimens in AF and PCI? (4)

- Although twice-daily low-dose Rivaroxaban (2.5 mg or 5 mg b.i.d.) has been used with some benefit in ACS, there are no data on ACS relating to the dose of rivaroxaban used for anticoagulation in AF (20 mg o.d.).

- Apixaban, used in the stroke prevention dose (5 mg b.i.d.) in the ACS setting in combination with aspirin plus clopidogrel, was associated with no reduction in cardiovascular events but an excess of major bleeding.
Take-home messages

- In AF patients, presenting for PCI always pay attention to clinical characteristics, especially bleeding risk.
- Use the most straightforward PCI technique and stent type, minding the coronary anatomy and risk for restenosis / stent thrombosis.
- Do not underestimate the strict targets of INR (2,0-2,5) in patients on OAC+DAPT/APT.
- Mind the timelines for DAPT discontinuation / reduction.
- There is no hard data to support use of NOAC with DAPT in AF patients.
Acknowledgements

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Thank you for your attention