Tips for Management of Patients Who Require Oral Anticoagulation for Atrial Fibrillation and Post-PCI Antiplatelet Therapy

Dinh Duc Huy, MD, FSCAI
Tam Duc Heart Hospital
Major bleeding was associated with a significant increase in in-hospital mortality, regardless of bleeding site

- 3.3 million PCI procedures (2004–2011 Registry)
- Bleeding: most common non-cardiac complication
- Antithrombotic therapy that minimizes the risk of bleeding complications therefore might be expected to result in better short- and long-term clinical outcomes after PCI

Chhatriwalla et al. JAMA 2013
Up to 10% of patients undergoing PCI with stenting have an indication for oral anticoagulation (OAC).

- atrial fibrillation (AF)
- venous thromboembolism (VTE)
- mechanical valves

Post-PCI dual antiplatelet therapy (DAPT) plus OAC = Triple therapy (TT)

- is associated with a significant increase in the risk of bleeding
- doubles the risk of serious bleeding and transfusions post-PCI
- is associated with increased mortality
Pre-PCI Considerations

1. **Assess the need for PCI.** Does the patient really need a stent?
   - 2017 AUC for PCI (ACC/AHA/SCAI)
   - 2018 ESC guidelines for myocardial revascularization

2. **Assess the risk of stroke**
   - Long-term OAC is recommended for CHA$_2$DS$_2$-VASc
   - $\geq 2$ in men and $\geq 3$ in women

3. **Assess the risk of bleeding**
   - HAS-BLED score of $\geq 3$ is associated with a high bleeding risk
**CHA\textsubscript{2}DS\textsubscript{2}-VASc**

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/left ventricular dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

**HAS-BLED**

<table>
<thead>
<tr>
<th>HAS-BLED risk criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (SBP &gt;160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding (history or predisposition)</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (e.g. age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

*Lip G et al. Stroke 2010;41:2731–8;*  
*Pisters R et al. Chest 2010;138:1093–100*
Considerations During PCI

1. Use radial access preferentially over femoral access for PCI
   • patients who require post-PCI anticoagulation

2. Use newer generation DES vs. BMS
   • Four weeks of DAPT in HBR patients (LEADERS FREE)
   • safety confirmed
   • superior efficacy

3. Adequate clopidogrel and aspirin loading pre-PCI in all patients

4. Continue of aspirin until hospital discharge
   (even in patients in whom DT is planned on discharge)
Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D.,

1-month DAPT in HBR?

- Age ≥75 yr
- Oral anticoagulation planned to continue after PCI
- Hemoglobin <11 g/l or transfusion within 4 wk before randomization
- Platelet count <100.000/mm³
- Hospital admission for bleeding in previous 12 mo
- Stroke in previous 12 mo
- Previous intracerebral hemorrhage
- Severe chronic liver disease
- Creatinine clearance <40 ml/min
- Cancer in previous 3 yr
- Planned major surgery in next 12 mo
- Glucocorticoids or NSAID planned for >30 days after PCI
- Expected nonadherence to >30 days of dual antiplatelet therapy

Đặc điểm bệnh nhân có nguy cơ XH cao
- ≥75 tuổi
- Cần tiếp tục dùng kháng đông uống sau PCI
- Hb <11 g/l hoặc có truyền máu trong vòng 4 tuần trước phân nhóm ngẫu nhiên
- Tiêu cần <100.000/mm³
- Nhập viện vì xuất huyết trong vòng 12 tháng trước
- Tiền căn đột quỵ trong vòng 12 tháng
- Tiền căn xuất huyết não
- Suy gan nặng
- Độ lọc cầu thận <40ml/phút
- Bệnh lý ung thư trong vòng 3 năm trước
- Có kế hoạch đại phẫu trong 12 tháng tới
- Cần dùng corticoid hoặc NSAID kéo dài hơn 30 ngày sau PCI
- Khả năng tuần tự DAPT > 30 ngày kém
Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

1-month DAPT in HBR patients

Safety & Efficacy

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 Oriban, Freek W A Verheugt, Johannes C Kelder, Bart J G J De Smet, Jean-Paul Henman, Tom Adriaenssens, Matthias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijssen, Arnaud W van ‘t Hof, Juriën M ten Berg, for the WOEST study investigators

- Open-label, multi-centre, randomised, controlled trial
- 15 centers in Belgium and the Netherlands
- Clopidogrel+OAC vs. Clopidogrel+Aspirin+OAC
- **PE- any bleeding within 1 year of PCI**

Less bleeding with double therapy (Clopidogrel+OAC)

Omission of aspirin from TT resulted in a highly significant 25% absolute RR (NNT =4)

Lancet 2013; 381: 1107–15
PIONEER AF-PCI: lower rate of bleeding risk (PE) in both rivaroxaban groups vs TT group

Composite of bleeding events

Group 3: Triple therapy 26.7%
Group 2: R2.5 + DAPT 18.0%
Group 1: R15/10 + Clopi. 16.8%

PIioneer AF-PCI: similar rates of thromboembolic events

MACE = composite of CV death, MI, and stroke

The study was not powered to show superiority or non-inferiority between treatments in efficacy endpoints.

RE-DUAL PCI: Significantly lower rates of bleeding risks with dabigatran DT vs. TT


ISTH major bleeding event
• Symptomatic bleeding in a critical area or organ, and/or
• Bleeding associated with reduced haemoglobin ≥2 g/dL (1.24 mmol/L) or transfusion of ≥2 units of blood or packed cells and/or
• Fatal bleed

CRNM bleeding event
Not meeting criteria for a major bleed but prompts ≥1 of:
• Hospital admission
• Physician-guided medical or surgical treatment
• Physician-guided change, interruption (≥1 dose) or discontinuation of study drug
REDUAL- PCI: Dabigatran DT was non-inferior to Warfarin TT in efficacy endpoint

Composite endpoint of death or thromboembolic event

(MI, stroke or systemic embolism) or unplanned revas. (PCI/CABG)

HR: 1.04 (95% CI: 0.84–1.29)  
Non-inferiority P=0.005

### A Safety: Major and Minor Bleeding Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dual Therapy</th>
<th>Triple Therapy</th>
<th>Odds Ratio (95% CI)</th>
<th>z Score</th>
<th>Relative Weight</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOEST</td>
<td>54/279</td>
<td>126/284</td>
<td>0.30 (0.21–0.44)</td>
<td>-6.22</td>
<td>29.1</td>
<td>&lt;0.001</td>
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<tr>
<td>PIONEER AF-PCI</td>
<td>109/696</td>
<td>167/697</td>
<td>0.59 (0.45–0.77)</td>
<td>-3.86</td>
<td>34.1</td>
<td>&lt;0.001</td>
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<tr>
<td>RE-DUAL PCI</td>
<td>305/1744</td>
<td>196/764</td>
<td>0.61 (0.50–0.75)</td>
<td>-4.68</td>
<td>36.8</td>
<td>&lt;0.001</td>
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<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.49 (0.34–0.72)</td>
<td>-3.70</td>
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<td>&lt;0.001</td>
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<tr>
<td>I²=82.06</td>
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</table>

**LESS BLEEDING**

### B Efficacy: Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dual Therapy</th>
<th>Triple Therapy</th>
<th>Odds Ratio (95% CI)</th>
<th>z Score</th>
<th>Relative Weight</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOEST</td>
<td>31/279</td>
<td>50/284</td>
<td>0.58 (0.36–0.95)</td>
<td>-2.18</td>
<td>25.5</td>
<td>0.03</td>
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<tr>
<td>PIONEER AF-PCI</td>
<td>41/694</td>
<td>36/695</td>
<td>1.15 (0.72–1.82)</td>
<td>0.59</td>
<td>27.0</td>
<td>0.55</td>
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<tr>
<td>RE-DUAL PCI</td>
<td>239/1744</td>
<td>131/764</td>
<td>0.77 (0.61–0.97)</td>
<td>-2.23</td>
<td>47.47</td>
<td>0.03</td>
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<tr>
<td>Overall</td>
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<td>0.80 (0.58–1.09)</td>
<td>-1.40</td>
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<td>0.16</td>
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<td>I²=51.17</td>
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</tbody>
</table>

**SIMILAR MACE**

*Piccini JP, N Engl J Med 2017*
AUGUSTUS: Less bleeding with Apixaban and without Aspirin (DT) in AF and recent ACS or PCI patients treated with P2Y12 inhibitor

- TT: significant increase the risk of bleeding at 6 months (HR 1.89, NNH=14)
- Omission of aspirin lowered bleeding risk by 47%
AUGUSTUS: Less hospitalizations without significant differences in ischemic risk with Apixaban and without Aspirin (DT)
**ESC GUIDELINES 2017: strategies to avoid bleeding**

- Assess ischaemic and bleeding risks using validated risk predictors (e.g. \( \text{CHA}_2\text{DS}_2\text{-VASc} \), ABC, HAS-BLED) with a focus on modifiable risk factors.

- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.

- Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.

- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.

- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.

- Clopidogrel is the \( \text{P}2\text{Y}_{12} \) inhibitor of choice.

- Use low-dose (\( \leq 100 \text{ mg daily} \)) aspirin.

- Routine use of PPIs.
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)

Patients with an indication for oral anticoagulation undergoing PCI

Concerns about ischaemic risk prevailing

Concerns about bleeding risk prevailing

Time from treatment initiation

1 mo.

3 mo.

6 mo.

12 mo.

Beyond 12 mo.

A = Aspirin
C = Clopidogrel
O = Oral anticoagulation
North American Expert Consensus Antithrombotic Therapy for AF patients Treated with OAC Undergoing PCI

<table>
<thead>
<tr>
<th>Time from PCI</th>
<th>Default strategy</th>
<th>Patients at high ischemic/thrombotic and low bleeding risks</th>
<th>Patients at low ischemic/thrombotic or high bleeding risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-PCI</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy (OAC + DAPT)</td>
</tr>
<tr>
<td>1 month</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Triple Therapy up to 1 month (OAC + DAPT)</td>
<td>Double Therapy up to 6 months (OAC + SAPT)</td>
</tr>
<tr>
<td>3 months</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>OAC</td>
</tr>
<tr>
<td>12 months</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>OAC</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>OAC</td>
<td>OAC</td>
<td>OAC</td>
</tr>
</tbody>
</table>

OAC: prefer a NOAC over VKA if no contraindications
SAPT: prefer a P2Y12 inhibitor over aspirin
Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel
Consider SAPT in addition to OAC after >12 mo. only in select patients at high ischemic/thrombotic and low bleeding risks

*Circulation. 2018;138:527–536*
<table>
<thead>
<tr>
<th>Patient type</th>
<th>Treatment Regimens</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average ischemic &amp; bleeding risk</td>
<td>DT (C + O) up to 12 months</td>
<td>North American Expert Consensus update recommendation (2018)</td>
</tr>
<tr>
<td>(default strategy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High ischemic risk (ACS) &amp; low bleeding risk</td>
<td>TT x 1 month followed by DT (C + O) x 11 months</td>
<td>North American Expert Consensus update recommendation (2018)</td>
</tr>
<tr>
<td></td>
<td>TT x 6 months followed by DT (C + O or A + O) x six months</td>
<td>ESC recommendation IIa, LOE B (2017)</td>
</tr>
<tr>
<td>Patient type</td>
<td>Treatment Regimens</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>TT x 1 month</td>
<td>ESC recommendation IIa, LOE B (2017)</td>
</tr>
<tr>
<td></td>
<td>followed by DT (C + O or A + O) x 11 months or less</td>
<td>ESC recommendation IIa, LOE A (2017)</td>
</tr>
<tr>
<td></td>
<td>DT (C + O) x 12 months</td>
<td></td>
</tr>
<tr>
<td>High ischemic &amp; high bleeding risk</td>
<td>No specific recommendations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use clinical judgment and shared decision-making</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider referral for left atrial appendage occlusion</td>
<td></td>
</tr>
</tbody>
</table>
Antiplatelet agent considerations

1. Most patients enrolled in recent studies were taking clopidogrel
   Ticagrelor was used as part of DT in 12 percent of patients in RE-DUAL PCI.
   Prasugrel and ticagrelor should not be used as a component of TT (Class III-harm ESC guidelines)

2. Aspirin dose should typically ≤ 81 mg

3. Consider discontinuation of the antiplatelet agent from dual therapy
   after one year in patients with low ischemic risk
   after six months in patients with a high bleeding risk
1. **Using a DOAC instead of warfarin if there is no contraindication**

   Continue warfarin if the patient was tolerating it or if Creat. Clearance < 30 ml/min

   INR target: 2-2.5

2. **There is no role of withholding OAC in patients with AF post-PCI**

   No role of DAPT for AF patients

3. **DOACs are not approved for “valvular AF”**

   AF in the presence of a mechanical heart valve or moderate-to-severe mitral stenosis.
2018 EHRA Guidelines

Elective PCI with newer generation DES

ACS with PCI

Factors to shorten combination therapy
- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE ≥140 if ACS)

Factors to lengthen combination therapy
- First-generation DES
- High atherothrombotic risk (scores as above; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk
### Table I  Scientific rationale of recommendations

<table>
<thead>
<tr>
<th>Definitions where related to a treatment or procedure</th>
<th>Consensus statement instruction</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial or is supported by strong observational evidence and authors’ consensus (as indicated by an asterisk).</td>
<td>‘Should do this’</td>
<td><img src="image" alt="Green Heart" /></td>
</tr>
<tr>
<td>General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable.</td>
<td>‘May do this’</td>
<td><img src="image" alt="Yellow Heart" /></td>
</tr>
<tr>
<td>Scientific evidence or general agreement not to use or recommend a treatment or procedure.</td>
<td>‘Do not do this’</td>
<td><img src="image" alt="Red Heart" /></td>
</tr>
</tbody>
</table>

*This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I-HII) and level of evidence (A, B, and C) to recommendations.*
When dabigatran is used as part of DAT, the standard doses of 150 mg bid should be used to reduce the risk of ischaemic events.

- As per prescribing label, dabigatran 110 mg bid can be considered in elderly patients, concomitant when Pgp inhibitors (e.g. verapamil) are used, and in patients with high bleeding risk.
- Both dabigatran 150 mg or 110 mg bid have been shown to be non-inferior (and in the case of 150 mg bid, superior) to warfarin for stroke prevention in AF.

When rivaroxaban is used as part of DAT, reduced dose 15 mg od should be considered.

- The efficacy with respect to stroke prevention of this reduced dose in this population has not been sufficiently evaluated.

When apixaban or edoxaban are used as part of TAT or DAT, the standard dose (5 mg bid and 60 mg od, respectively, unless label-guided dose reduction is indicated) should be selected pending results of ongoing trials.
Key messages

1. AF plus ACS/PCI: challenge clinical scenario
   - risk of embolic event (CHA2DS2-VASc)
   - bleeding (HAS-BLED)

2. Dual therapy (NOACs + Clopidogrel) seems to be
   - safe (reduce risk of bleeding)
   - efficacy (non-inferiority for thromboembolic events)

3. Tips for lower bleeding
   - use of PPIs for gastric protection, avoiding NSAIDs and alcohol
   - avoidance of supra-therapeutic INR
   - blood pressure control
   - adjustment of NOAC dose based on creatinine clearance
   - closer monitoring of patients on TT and those with a HAS-BLED score >3
Thank you!