Άννα Κωστοπούλου
Επιμελήτρια Α
Ωνάσειο Καρδιοχειρουργικό Κέντρο
Τμήμα Ηλεκτροφυσιολογίας και Βηματοδότησης
Experts consensus

- Protocols- guidelines based basically on the pharmacokinetics of the anticoagulants VKAs& NOACs
- Few randomized studies
VKA mechanism- vitamin K antagonists

Warfarin

Vitamin K

Vitamin K hydroquinone

Inactive proteins
Factors II, VIII, IX, X
Proteins C, S, and Z

Activated proteins

Vitamin K-dependent carboxylase

Vitamin K epoxide

Annu. Rev. Med. 61:63–75
### Hepatic metabolism

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life</th>
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<tbody>
<tr>
<td>II</td>
<td>42-72 hours</td>
</tr>
<tr>
<td>VII</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>IX</td>
<td>21-30 hours</td>
</tr>
<tr>
<td>X</td>
<td>27-48 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>60 hours</td>
</tr>
</tbody>
</table>

- **T1/2 warfarin**: 36-42 h
- **T1/2 acenocoumarol**: 8-11 h
NOACs
NOAC metabolism

Dabigatran
- Esterase-mediated hydrolysis
- Bio-availability: 3-7%
- $t_{1/2} = 12-17h$

Rivaroxaban
- Bio-availability: 66% (without food), >80% (with food)
- $t_{1/2}$:
  - Young: 5-9h
  - Elderly: 11-13h

Apixaban
- Bio-availability: 50%
- $t_{1/2} = 12h$

Edoxaban
- Bio-availability: 62%
- $t_{1/2}$:
  - Young: 9-11h
  - Elderly: ~50%

Question: 65 year old pt

• hypertensive, old TIA, persistent AFib under NOACs normal dose, normal renal function

• Recent diagnosis of colon Ca

• Sent by his general surgeon for Instructions for anticoagulation prior to surgery
Steps

1) Evaluation of Thrombotic risk
2) Evaluation of hemorrhagic risk
3) Discontinuation
4) Bridging
5) Reinitiating
1) Evaluation of Thrombotic risk

- **Valvular** prosthetic mechanic valves high- except AV bileaflet

- **Non valvular indications** scoring systems

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Congestive heart failure (or Left ventricular systolic dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension: blood pressure consistently above 140/90 mm Hg (or treated hypertension on medication)</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>Prior Stroke or TIA or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (ie, female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Low** 1-4 annual stroke risk <5% no prior TE

**Moderate** 5-6 risk 5-10% or prior TE more than 3m previously

**High** 7+ risk >10% or TE within 3 months
2) Evaluation of bleeding risk

- Patient bleed risk
  - High
  - Intermediate
  - Low

Scores HEMORR2HAGES and HAS-BLED
Procedural risk - a lot of disagreement

- **High risk**: cardiovascular, orthopedic, head and neck cancer or urological in nature, or those >45 min in length.
- **Low risk**: procedures anticipated to be <45 min, cutaneous, or relatively straightforward such as a cholecystectomy.
- **Unpredictable or uncertain**: ie biopsy hysterectomy, knee arthroplasty
3) Interruption

- Interrupt in pt with intermediate or high bleeding risk in procedures w hemorrhagic risk

- **clinical judgement**
- in the cases with **unpredictable risk**
  
  **pt** or procedure related
VKAs

- In all pts INR 5-7 days prior to procedure to identify pt with >3 irrelatively to if anticaogulation will be interrupted or not - repeat 24 h before

- **Warfarin** 3-5 depending on INR
- Shorter if known to decay earlier
- **Less for coumadin 3-4**

- Comparisons in few studies 1 randomized

Garcia DA Arch Intern Med 2008
• Strategy based on pharmakokinetics and the 4 studies
• PAUSE- ongoing prospective parallel for all 3 NOACs

High risk = 3 days no additional test
4) Bridging

- Bridged vs non bridged
- No difference in thromboembolic events
- Bridged= increased risk of major bleeding
  1 randomized study 5 other nonrandomized and and reviews
- NOAC bridging increases bleeding w/o decreasing embolic events

Eijgenraam et al, 2013  
Siegal et al 2012
Consider bridging

<table>
<thead>
<tr>
<th>VTE</th>
<th>Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Patients with a previous stroke/TIA in last 3 months. Patients with a previous stroke/TIA and three or more of the following risk factors: • Congestive cardiac failure • Hypertension (&gt;140/90 mmHg or on medication) • Age &gt;75 years • Diabetes mellitus</td>
</tr>
<tr>
<td>MHV</td>
<td>MHV patients other than those with a bileaflet aortic valve and no other risk factors</td>
</tr>
</tbody>
</table>
VKA- How to bridge???
5) Reinitiating

- **VKA** Early Resumption after 24 hour with at usual dose attained therapeutic INR in **5.1** days vs 4.6 with double dose for 2 days

- VKA can be resumed within first 24 hours at **usual dose** in most pt w/o parenteral heparin **when oral intake is permitted**

- In high risk pt for stroke or thromboembolism parenteral agent may be used

**NOACs Predictable weaning fast effect peri-procedural bridging not needed**

Safety of early reinitiation on day 1 with low dose and then escalation or in high risk after 48-72h with good hemostasis and postop assessment

1.8 hemorrhage 0.2% thrombosis 30 day
Assumptions

• These algorithms assume that the patient is not taking concomitant antiplatelet agents

• Used for elective planned procedures, not those occurring urgently or emergently.
Emergencies-Antidotes

- For VKA Vit K oral vitamin K
- Clotting factors

No safe test to evaluate residual antithrombotic effect of NOACS developing

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Reversal agent characteristics</th>
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<tbody>
<tr>
<td>Specific reversal agent</td>
<td>Molecular entity</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>Recombinant protein derived from human FXa [8,13]</td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>Fully humanized monoclonal antibody fragment (Fab) [38]</td>
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DTI = direct thrombin inhibitor; FIIa = factor IIa; FXa = factor Xa; IV = intravenous; LMWH = low-molecular-weight heparin
Conclusions

**Figure 1: Typical Managers of Periprocedural Anticoagulation**

**During**
- Cardiologist: 56%
- Physician performing procedure: 36%
- Primary Care physician: 28%
- Anticoagulation service: 27%
- Pharmacist: 15%
- Nurse practitioner: 11%
- Other: 5%
- Not sure: 2%

**After**
- Cardiologist: 47%
- Primary care physician: 34%
- Anticoagulation service: 28%
- Physician performing procedure: 21%
- Pharmacist: 14%
- Nurse practitioner: 11%
- Other: 4%
- Not sure: 2%
Consider VKA vs. DOAC, evaluate patient bleed risk, evaluate procedural bleed risk (very clinically relevant, low, intermediate, high or uncertain), consider additional information and use clinical judgment.

Consider VKA, FXa Inhibitor or DTI, and either INR or CrCl.

Consider VKA vs. DOAC, evaluate thrombotic risk balanced by patient bleed risk, consider additional information, and use clinical judgment.

Evaluate CrCl and patient allergies.

Consider post-procedure bridging plan, VKA vs. DOAC, procedure type (cardiac valve, intraportal, intracranial), and evaluate post-procedure bleed risk, bleeding complications, hemostasis, and toleration of oral medications.

CrCl = creatinine clearance; DOAC = direct oral anticoagulant; DTI = direct thrombin inhibitor; FXa = factor Xa; INR = international normalized ratio; VKA = vitamin K antagonist
Ευχαριστώ για την προσοχή σας