Αντιπηκτική αγωγή μετά από αιμορραγία

Παν Στρέμπελας
Β’ Καρδιολογική Κλινική ΝΝΑ
Αντιηλικική αγωγή μετά από αιμορραγία
Who?
Patients on anticoagulation therapy

• **Atrial fibrillation**

  • Prosthetic heart valves
  • LVAD
  • LV, LA thrombus
  • Pulmonary embolism, DVT
  • Other: tako-tsubo, non compaction CM, recurrent or cancer associated DVT
Major bleeding in RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY DBG</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>ROCKET-AF RVX</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>ARISTOTLE ABX</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>ENGAGE-AF EDX</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

2.3-3.6%

ESC AFIB 2016
Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients

- Overall major bleeding rate 4.5%
- Abixaban lower bleeding rate than
  - Rivaroxaban HR 1.49,
  - Dabigatran HR 1.17,
  - Warfarin HR 1.23
- Non persistence
  - Warfarin/dabigatran

J Am Heart Assoc. 2017
Bleeding severity

• **Bleeding in a critical site**
  • (intracranial and other CNS-intraspinal, intra-abdominal, retroperitoneal, thoracic, intramuscular, that compromise organ function).

• **Hemodynamic instability**
  • (BP< 90mmHg, BP fall>40mmHg, oliguria <0,5ml/Kg/hr)

• **Overt bleeding** with Hb drop >2g/dL or requiring ≥ 2 packed RBCs

Major bleeding if ≥1 factors, or non-major
### Type of Major Bleeding

<table>
<thead>
<tr>
<th>Type of Major Bleeding</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>1022 (42)</td>
</tr>
<tr>
<td>Renal/urinary</td>
<td>454 (19)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>399 (17)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>276 (11)</td>
</tr>
<tr>
<td>Anemia</td>
<td>232 (10)</td>
</tr>
<tr>
<td>Pericardial</td>
<td>16 (1)</td>
</tr>
<tr>
<td>Ocular</td>
<td>19 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2418 (100)</strong></td>
</tr>
</tbody>
</table>
Type of bleeding-type of OAC

- ICH 0.6% NOACs vs 1.3% VKA
- GI Bleeding 2.5% NOACs vs 2% VKA
Risk of major bleeding

ICH: 43.2%
Non ICH: 9.2%

14.9% mortality in 30 days

Hazard Ratio

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Stroke/MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>121</td>
<td>22</td>
</tr>
<tr>
<td>Non ICH</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
Management of bleeding

• Supportive measures
• Fluid replacement
• Blood transfusion
• Control of hemorrhage: manual compression, endoscopy, surgery
• Reversal agents
# Reversal agents

<table>
<thead>
<tr>
<th>VKA (warfarin, coumadin)</th>
<th>DTI (dabigatran)</th>
<th>Factor Xa Inhibitors (abixaban, rivaroxaban, edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F-PCC</td>
<td>Idarucizumab 5gr IV</td>
<td>4F-PCC</td>
</tr>
<tr>
<td>Doses according to INR or fixed doses according to bleeding severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFP if no PCC available</td>
<td>4F-PCC if idarucizumab is not available</td>
<td>aPCC if 4F-PCC is not available</td>
</tr>
<tr>
<td></td>
<td>aPCC if 4F-PCC is not available</td>
<td>Activated charcoal if ingestion&lt; 2-4 hr</td>
</tr>
<tr>
<td>Activated charcoal if ingestion&lt; 2-4 hr</td>
<td>Activated charcoal if ingestion&lt; 2-4 hr</td>
<td>Andexnet (on study - ANNEXA-4)</td>
</tr>
</tbody>
</table>

**Ciraparantag** (under investigation)
Reversal-VKA

- PCC (prothrombin complex concentrates): 4FPCC, aPCC,
  - 25-fold concentration of clotting factors vs plasma
  - Dosing according to INR (INR 2-4 25U/Kg, 4-6 35 U/Kg, >6 50 U/Kg max 5000 U)

- Plasma
  - Require ABO compatibility
  - Large volume infusion, allergic reactions

- Vit K
  - Not immediate (4-6 hrs) correction require plasma /PCC
  - Allergic reactions
Reversal - Dabigatran

- Idarucizumab (Praxibind) 2,5 mgX2 IV (FDA approved-RE-VERSE AD study)
- PCCs FFP mixed results - may help
- 35% bound to plasma protein
- Hemodialysis may remove 50-57% of drug within 4hrs
- Activated charcoal if <2hr of ingestion
Reversal -FXa inhibitors
Rivaroxaban/Abixaban/Edoxaban

- Andexanet a reversal agent in a phase 3 study ANNEXA-4
  - interim analysis: 79% improved clinical hemostasis, 18% thrombotic events - NEJM 2016

- PCCs and aFVII may improve coagulation parameters but no data for clinical improvement

- Highly bound to plasma proteins- dialysis ineffective

- Activated charcoal if <2hr of ingestion

- Ciraparartrang for FXa/ FII inhibitors under investigationn
Reinstitution of anticoagulation therapy after major bleeding event
Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis
Bleeding risk

Thromboembolic risk

• Need for long term AC therapy
• Concomitant use of anti platelet agents
• Dosage adjustment (high INR - Renal Failure)
• Bleeding characteristics
Bleeding risk

- Risk scores: HASBLED, ABC, ORBIT, HEMORR2HAGES, ATRIA

- Bleeding characteristics:
  - site critical/non critical,
  - type (traumatic, spontaneous),
  - source (identified/treated), planned procedure
- ABC, HASBLED the most predictive, especially for ICH

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong></td>
<td><strong>Hypertension</strong>: (uncontrolled, &gt;160 mmHg systolic)</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td><strong>Abnormal renal function</strong>: Dialysis, transplant, Cr &gt;2.26 mg/dL or &gt;200 µmol/L <strong>Abnormal liver function</strong>: Cirrhosis or Bilirubin &gt;2x Normal or AST/ALT/AP &gt;3x Normal</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td><strong>Stroke</strong>: Prior history of stroke</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>Bleeding</strong>: Prior Major Bleeding or Predisposition to Bleeding</td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>Labile <strong>INR</strong>: (Unstable/high INR), Time in Therapeutic Range &lt; 60%</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>Elderly: Age &gt; 65 years</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Prior Alcohol or Drug Usage History (≥ 8 drinks/week) Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>Biomarkers</strong> Growth differentiation factor-15 (GDF-15), High-sensitivity cardiac troponin T (cTnT-hs) Haemoglobin</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td><strong>Clinical History</strong>: Prior Bleeding</td>
</tr>
<tr>
<td>Risk score</td>
<td>Risk category</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>ABC</td>
<td>Low &lt;1%</td>
</tr>
<tr>
<td></td>
<td>Intermediate 1-2%</td>
</tr>
<tr>
<td></td>
<td>High &gt;2%</td>
</tr>
<tr>
<td>HASBLED</td>
<td>Low 0-1 points</td>
</tr>
<tr>
<td></td>
<td>Intermediate 2-3 points</td>
</tr>
<tr>
<td></td>
<td>High ≥4 pts</td>
</tr>
</tbody>
</table>

Zulkify Am J Cardiol Oct 2017 Review
# High thrombotic risk

## Indication

<table>
<thead>
<tr>
<th>Mechanical valves</th>
<th>+ risk factors AF, HF, Stroke /TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caged ball, titing disk</td>
</tr>
<tr>
<td>AF</td>
<td>CHADS score&gt;4</td>
</tr>
<tr>
<td></td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td></td>
<td>Stroke/TIA within 3 mon</td>
</tr>
<tr>
<td>VTE</td>
<td>&lt;3mon</td>
</tr>
<tr>
<td></td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td>Cancer associated VTE</td>
</tr>
</tbody>
</table>

## LVAD

[2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants]
Bleeding risk

Thromboembolic risk

- Need for long term AC therapy
- Concomitant use of anti platelet agents
- Dosage adjustment (high INR - Renal Failure)
- Bleeding characteristics
Need for long term AC therapy?

- AF CHA2DS2-VASc score ≤1
- VTE prophylaxis
- VTE or Bioprosthetic heart valve >3mon
- Large ant MI w/o visible thrombus
- Takotsubo CMPathy recovered
DAPT+OAC

• DAPT on top of OAC **2 to 3 fold increase** of bleeding complications  
  *Eur HJ 2013*

• Reevaluate the need of triple therapy

• Data from recent studies PIONEER-AF PCI, REDUAL suggest lower incidence of bleeding events with dual therapy (1 anti platelet + OAC) ,  *NEJM 2016, NEJM 2017*

• Clopidogrel is the PY12 inhibitor of choice, limited data on prasugrel and ticagrelor.  *ESC DAPT Update 2017*
If AF and CHA2DS2-VASc < 1↓
DAPT
ESC management of bleeding 2017
Other reversible factors

- Control of High BP
- High INR -> consider switch to NOAC
- Renal failure consider dose adjustment switch to other NOAC or VKA
- Concomitant drug use (antifungal, antiretroviral, amiodarone, diltiazem, verapamil)
Timing

• Clinical judgment bleeding vs thrombotic risk

• Restart after hemostasis is achieved and patient is clinically stable -
  • within 1 week ESC management of bleeding 2017

• Consider parenteral AC with short half life (UFH IV)

• Consider prophylactic doses of LMWH and titration to therapeutic doses if stable

• Other specialties opinion
Type of bleeding - ICH

- Lobar or subdural high risk for rebleeding
- Strict control of high BP (goal SBP<140 mmHg)
- Restart after 4 weeks - data only for VKA
  - AHA/ASA Guidelines for ICH 2015
  - 4-8 weeks Afib Guidelines ESC 2016
- NOACs preferable to VKA
  - ESC management of bleeding 2017
- Traumatic brain injury same as ICH
  - Circulation 2017
OAC after Stroke

Patient with atrial fibrillation and acute TIA or ischaemic stroke
Exclusion of intracerebral bleeding by CT or MRI

- TIA
- Mild stroke (NIHSS <8)
- Moderate stroke (NIHSS 8–15)
- Severe stroke (NIHSS ≥16)

Consider additional clinical factors favouring early / delayed initiation of OAC

Factors favouring early initiation of OAC:
- Low NIHSS (<8):
- Small/no brain infarction on imaging
- High recurrence risk, e.g. cardiac thrombus on echo
- No need for percutaneous endoscopic gastrostomy
- No need for carotid surgery
- No haemorrhagic transformation
- Clinically stable
- Young patient
- Blood pressure is controlled

Factors favouring delayed initiation of OAC:
- High NIHSS (≥8):
- Large/moderate brain infarction on imaging
- Needs gastrostomy or major surgical intervention
- Needs carotid surgery
- Haemorrhagic transformation
- Neurologically unstable
- Elderly patient
- Uncontrolled hypertension

Start OAC
- 1 day after acute event
- 3 days after acute event
- 6 days after acute event
- 12 days after acute event

ESC Afib Guidelines 2016
Type of bleeding - GI

- Most common bleeding

- Restarting AC -> Lower risk of TE HR 0.68, and death HR 0.76 and NS recurrence of GI bleeding HR 1.2.


- Reinitiation once bleeding has been controlled

  - JACC 2017
After surgery

- Low postprocedural bleeding risk -> start AC after 24 hrs

- High post procedural bleeding risk -> start AC after 48-72 hrs

- Bridging with LMWH is associated with an increased risk of bleeding and no decrease in thrombotic events BRIDGE study NEJM 2015

- Consider bridging only if thromboembolic risk is high *with VKA- not for NOACs
High TE risk + high bleeding risk

• Non-pharmacological therapies
  • LAA closure
  • IVC filter
• Patient preference
• Other specialties opinion
LAA closure

• Intravascular device (WATCHMAN)

• PROTECT-AF showed non-inferiority and non-superiority vs warfarin

• Requires at least 45 days of OAC

JAMA Nov 2014
LAA closure

- Thoracoscopic closure device
- Does not require OAC
IVC filter

- Only in recent proximal DVT + absolute contraindication for OAC - removal prior to hospital discharge
- Increase incidence of recurrent DVT no survival benefit
  - PREPIC study Circ 2005
## Patient engagement in decision making

<table>
<thead>
<tr>
<th>Factors to Consider</th>
<th>Discussion Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Discussion of reinitiation of anticoagulation should be done in advance of restarting to give the patient time to formulate questions</td>
</tr>
<tr>
<td>Associated risks</td>
<td>Clinical and site-specific signs of bleeding for which the patient should remain vigilant (e.g., melena after a GI bleed)</td>
</tr>
<tr>
<td></td>
<td>Recurrent bleeding thrombotic event (personalized risk assessment if possible, e.g., CHA₂DS₂-VASc prediction of thromboembolism risk)</td>
</tr>
<tr>
<td></td>
<td>Discussion of the sequelae of a thromboembolic event (e.g., higher mortality for ischemic strokes with AF)</td>
</tr>
<tr>
<td>Associated benefits</td>
<td>Improved mortality with no increase in bleeding after certain types of bleeds on anticoagulant (e.g., GI bleeding)</td>
</tr>
</tbody>
</table>

### 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants
Conclusions

• Restarting anticoagulation after a bleeding event is based on clinical judgment considering thromboembolic vs bleeding risk

• Actions to correct reversible factors

• Consider non pharmacological measures

• Consider patient preference after adequate information