Intracranial haemorrhage and anticoagulation

Content

1. Relevance
2. Principles
3. Management
New AF - baseline therapy in the Garfield registry

1. NOACs prescription increasing, currently at 35%
2. VKA prescription decreasing, currently at 20%
3. Combination of OAC with AP similar (7%)

AP - anti-platelets; VKA - Vitamin-K antagonist;
NOAC - non-Vitamin-K antagonist oral anticoagulant

Steinberg BA et al. Am Heart J. 2017;194:132-140

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Reversal of Coagulopathy

**Why**

Intracerebral hemorrhage
Goal: prevention of hematoma expansion

**Who**

- VKA
- Dabigatran
- Factor Xa-Inhibitor

Relevant drug concentrations assumed?

Check on:
- time last taken: half-life time, dose
- liver function, renal function
- drug-drug interaction

INR > 1.2
Drug levels > 30ng/mL

Relevant drug concentrations assumed: Yes

**When**

- ?
- ?
- ?

**What**

- ?
- ?
- ?

Steiner T, Welz I J, Veltsch R Stroke 2017;48:1432-1437

Why: The problem is hematoma expansion in different clinical settings

<table>
<thead>
<tr>
<th>Spontaneous ICH</th>
<th>VKA-ICH</th>
<th>NOAC-ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30%*</td>
<td>≤ 54%*</td>
<td>≤ 38%*</td>
</tr>
</tbody>
</table>

Hematoma expansion is frequent

Hematoma expansion determines prognosis

ICH: Intracerebral hemorrhage; VKA: Vitamin K antagonist; * 33% of baseline volume
Peak and trough levels of OACs

<table>
<thead>
<tr>
<th></th>
<th>VKA</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak values (hrs)</td>
<td>—</td>
<td>2–3</td>
<td>1–4</td>
<td>2–4</td>
<td>1–2</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>Acenocumarol: 9 hours</td>
<td>Warfarin: 2 days</td>
<td>Phenprocoumon: 7 days</td>
<td>12–17</td>
<td>9 - 14</td>
</tr>
</tbody>
</table>


NOACs have a beneficial pharmacological profile compared with warfarin

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal excretion (%)</td>
<td>&lt;1</td>
<td>85</td>
<td>~33</td>
<td>27</td>
<td>~50</td>
</tr>
<tr>
<td>Interactions</td>
<td>Multiple</td>
<td>P-gp</td>
<td>CYP3A4 P-gp</td>
<td>CYP3A4 P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

Adapted from: Pradaxa®: EU SPC, 2015; Xarelto: EU SPC, 2015; Eliquis: EU SPC, 2015; Warfarin sodium: SPC, 2015; Savaysa US PI 2015
PT and aPTT sensitivities and costs

<table>
<thead>
<tr>
<th></th>
<th>PT Sensitivity</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>74% (95% CI, 70%-78%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>56% (95% CI, 47%-64%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>n.a.</td>
<td>98% [95% CI, 89%-100%]</td>
</tr>
<tr>
<td>Cost (Medicare fee schedule)</td>
<td>7.29 US$</td>
<td>11.23 US$</td>
</tr>
</tbody>
</table>

Recommendation:
- **Factor Xa-inhibitors**: If available use anti-Xa assay using a drug-specific calibrator
- **Dabigatran**: If available use dilute thrombin time

Plasma drug levels < 30 ng/mL: absence of a significant anticoagulant effect

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**Meta-Analysis of PCC-FFP trials**

Outcome: Mortality at day 90

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FFP Events</th>
<th>Total</th>
<th>PCC Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner 2016</td>
<td>8</td>
<td>23</td>
<td>5</td>
<td>27</td>
<td>32.5%</td>
<td>2.35 [0.64, 8.57]</td>
</tr>
<tr>
<td>Sarode 2013</td>
<td>10</td>
<td>103</td>
<td>4</td>
<td>109</td>
<td>38.0%</td>
<td>2.82 [0.86, 9.30]</td>
</tr>
<tr>
<td>Goldstein 2015</td>
<td>8</td>
<td>88</td>
<td>3</td>
<td>88</td>
<td>29.5%</td>
<td>2.83 [0.73, 11.06]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26</td>
<td>214</td>
<td>12</td>
<td>224</td>
<td>100.0%</td>
<td>2.67 [1.28, 5.58]</td>
</tr>
</tbody>
</table>

Total events: 26, 12

Heterogeneity: \( \chi^2 = 0.05, \) df = 2 (\( P = 0.97 \)); \( I^2 = 0\%

Test for overall effect: \( Z = 2.61 (P = 0.009) \)

**Management of ICH related to VKA**

**Prothrombin complex concentrate (PCC)**

<table>
<thead>
<tr>
<th>Indication threshold</th>
<th>Reversal agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 ≤ INR &lt; 2</td>
<td>PCC: 10 U/kg i.v.</td>
</tr>
<tr>
<td>2 ≤ INR</td>
<td>PCC: 50 U/kg i.v.</td>
</tr>
<tr>
<td></td>
<td>Vitamin-K: 10mg i.v.</td>
</tr>
</tbody>
</table>

Intracranial haemorrhage and anticoagulation

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EHRA Practical Guide 2018 on the management of bleeding recommends idarucizumab use in patients on dabigatran

Bleeding while using a NOAC

- Inquire about last NOAC intake
- Blood sample to determine CrCl, haemoglobin etc.
- Rapid coagulation assessment, incl. plasma drug levels (if available)

Mild bleeding
- Delay or discontinue next dose
- Reconsider concomitant medication
- Reconsider choice of NOAC and dosing

Non life-threatening major bleeding
- Supportive measures
  - Mechanical compression
  - Endoscopic haemostasis if GI bleed
  - Surgical haemostasis
  - Fluid replacement
  - RBC substitution if needed
  - Platelet substitution (if platelet count ≤60 x 10⁹/L)
  - Consider adjuvant tranexamic acid
  - Maintain adequate diuresis
  - Consider idarucizumab* haemodialysis (if idarucizumab is not available) for dabigatran

Life-threatening bleeding
- For dabigatran-treated patients, idarucizumab 5 g IV
- For FXa inhibitor-treated patients: andexanet alfa*

Otherwise, consider:
- PCC: 50 U/kg + 25 U/kg if indicated
- aPCC: 50 U/kg; max 200 U/kg/day

*Andexanet alfa is only approved in the USA

Adapted from Steffel et al. Eur Heart J 2018
Intracranial haemorrhage and anticoagulation

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Restart?
Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

Alessandro Biffi, MD, Joji B. Kuramatu, MD, Audrey Leasure, BS, Hooman Kamel, MD, Christina Kourkoulis, BS, Kristin Schwab, BA, Alison M. Ayres, BA, Jordan Elm, PhD, M. Edip Gurol, MD, MSc, Steven M. Greenberg, MD, PhD, Anand Viswanathan, MD, PhD, Christopher D. Anderson, MD, MMS, Stefan Schwab, MD, Jonathan Rosand, MD, MSc, Fernando D. Tostai, MD, PhD, Daniel Woo, MD, MS, Hagen B. Huttner, MD, and Kevin N Sheth, MD

Oral anticoagulation resumption and outcomes following intracerebral hemorrhage at 1 year

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All ICH</th>
<th>95% CI</th>
<th>p</th>
<th>Nonlobar ICH</th>
<th>95% CI</th>
<th>p</th>
<th>Lobar ICH</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.27</td>
<td>0.19–0.40</td>
<td>&lt;0.0001</td>
<td>0.25</td>
<td>0.14–0.44</td>
<td>&lt;0.0001</td>
<td>0.29</td>
<td>0.17–0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Favorable outcome, mRS = 0–3</td>
<td>4.15</td>
<td>2.92–5.90</td>
<td>&lt;0.0001</td>
<td>4.22</td>
<td>2.57–6.94</td>
<td>&lt;0.0001</td>
<td>4.08</td>
<td>2.48–6.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause stroke</td>
<td>0.47</td>
<td>0.36–0.64</td>
<td>&lt;0.0001</td>
<td>0.41</td>
<td>0.25–0.67</td>
<td>0.0004</td>
<td>0.51</td>
<td>0.37–0.76</td>
<td>0.0005</td>
</tr>
<tr>
<td>Recurrent ICH</td>
<td>1.20</td>
<td>0.95–1.58</td>
<td>0.21</td>
<td>1.17</td>
<td>0.89–1.54</td>
<td>0.27</td>
<td>1.26</td>
<td>0.88–1.71</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.44</td>
<td>0.29–0.66</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>0.21–0.74</td>
<td>0.004</td>
<td>0.48</td>
<td>0.25–0.75</td>
<td>0.003</td>
</tr>
</tbody>
</table>

OAT resumption is - in both non lobar and lobar ICH - associated with
- decreased mortality
- increased likelihood of favourble outcome
- Decreased likelihood of ischemic stroke
- but not of recurrent ICH

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*All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score.

Statistically significant.

CI = confidence interval; HR 5 hazard ratio; ICH 5 intracerebral hemorrhage; mRS 5 modified Rankin Scale.
Oral anticoagulation resumption and long-term outcomes (beyond 1 year (49 months)) following intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All ICH</th>
<th>Nonlobar ICH</th>
<th>Lobar ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>HR 0.32</td>
<td>0.15–0.66</td>
<td>0.002b</td>
</tr>
<tr>
<td>Favorable outcome, mRS = 0–3</td>
<td>3.99</td>
<td>1.76–9.05</td>
<td>0.001b</td>
</tr>
<tr>
<td>All-cause stroke</td>
<td>0.50</td>
<td>0.32–0.79</td>
<td>0.003b</td>
</tr>
<tr>
<td>Recurrent ICH</td>
<td>1.10</td>
<td>0.96–1.26</td>
<td>0.20</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.46</td>
<td>0.28–0.75</td>
<td>0.002b</td>
</tr>
</tbody>
</table>

OAT resumption is - in both non lobar and lobar ICH - associated with
- decreased mortality
- increased likelihood of favourable outcome
- decreased likelihood of ischemic stroke
- but not of recurrent ICH
- Similar to 1 year-results


Oral anticoagulation resumption and outcomes following lobar ICH related to possible versus probable CAA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Possible CAA</th>
<th>Probable CAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>HR 0.27</td>
<td>0.08–0.86</td>
</tr>
<tr>
<td>Favorable outcome, mRS 0–3</td>
<td>3.40</td>
<td>1.22–9.46</td>
</tr>
</tbody>
</table>

OAT resumption is - in both possible and probable CAA - associated with
- decreased mortality
- favourable outcome

-All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score.
-Statistically significant.
CI = confidence interval; HR 5 hazard ratio; ICH 5 intracerebral hemorrhage; mRS 5 modified Rankin Scale. Biffi A et al. Ann Neurol. 2017;82:755-765
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Restart?

How high is the risk of new ischemic and hemorrhagic events after restart of OAC?

Significantly increased rate of ischemic events if OAC not restarted

No clear increase of ICH recurrence if OAC restarted

Kuramatsu JB, et al. JAMA 2015;313:824-836
Survival Rates of patients with atrial fibrillation with and without OAC resumption

 ![Graph showing survival rates with and without OAC resumption](image)

Significant higher chance of survival if OAC is restarted


Intracranial haemorrhage and anticoagulation

**Restart OAC after ICH - Opinion:**

1. Restarting of OAC after and OAC-associated ICH is probably indicated when there is a clear indication OAC (AFib) and blood pressure control is sufficient and after CT or MRI-control demonstrated no abnormal degradation of ICH, and no massive CMBs / Siderosis, because retrospective data demonstrated a significant increased survival and fewer ischemic events when OAC was restarted but increased rated of recurrent ICH

2. Restarting should be considered between 14 days and 10 weeks after CT or MRI demonstrated no abnormal degradation of ICH

3. Alternatively: LAA-ooclusion can considered in case of clear contraindication for OAC