EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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EHRA Practical Guide on the use of new oral anticoaguants (NOAC) in patients with non-valvular atrial fibrillation

• This slide set is based on the following full text paper:
H. Heidbuchel; P. Verhamme; M. Alings; M. Antz; W. Hacke; J. Oldgren; P. Sinnaeve; A.J. Camm; P. Kirchhof.
Published by Oxford University Press, May 15, 2013. doi: 10.1093/europace/eut083

• An executive summary was published in:
H. Heidbuchel; P. Verhamme; M. Alings; M. Antz; W. Hacke; J. Oldgren; P. Sinnaeve; A.J. Camm; P. Kirchhof.
European Heart Journal 34: 2094-106 (2013)
Published by Oxford University Press, April 26, 2013

• Updated information, downloadable anticoagulation cards, and possibility for feedback are available via: www.NOACforAF.eu
The articles and related educational material (slide set, Web page, Key Message booklet, ...) were produced by and under the sole responsibility of the European Heart Rhythm Association, EHRA.

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The EHRA writing committee collaborated with medical experts from the different companies to assure data accuracy and completeness.
Advantages of new oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular AF

• predictable effect without need for monitoring
• fewer food and drug interactions
• more predictable half-life/elimination
• improved efficacy/safety ratio
Need for a practical guide

- 2010 ESC Guidelines (and the 2012 Update) do not detail the NOAC in specific clinical situations.¹,²
- Multiple physician tools supplied with each drug may be confusing.
- EHRA has now produced a practical guide to supplement AF guidelines.

2. Camm et al, Eur Heart J 2012; 33:2719-47
NOACs approved or under evaluation for prevention of systemic embolism or stroke in patients with non-valvular AF

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban *</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td>Direct thrombin</td>
<td>Activated factor</td>
<td>Activated factor</td>
<td>Activated factor</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td>Xa (FXa) inhibitor</td>
<td>Xa (FXa) inhibitor</td>
<td>Xa (FXa) inhibitor</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg BID</td>
<td>5 mg BID</td>
<td>60 mg QD</td>
<td>20 mg QD</td>
</tr>
<tr>
<td></td>
<td>110 mg BID</td>
<td>2.5 mg BID</td>
<td>30 mg QD</td>
<td>15 mg QD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 mg QD</td>
<td></td>
</tr>
<tr>
<td><strong>Phase III clinical trial</strong></td>
<td>RE-LY ¹</td>
<td>ARISTOTLE ²</td>
<td>ENGAGE-AF ⁴</td>
<td>ROCKET-AF ⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AVERROES ³</td>
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<td></td>
</tr>
</tbody>
</table>

* not yet approved by EMA


www.escardio.org/EHRA
1. Practical start-up and follow-up scheme for patients on NOACs

• Risk/benefit analysis: is a NOAC indicated?
• When choosing a NOAC, consider co-medications taken by patient.
• Consider co-medications such as PPI to reduce risk for gastro-intestinal bleeding.
• Carry information card: generic card could serve for all NOACs.
• Need to educate patient on importance of strict adherence to regimen – discontinuation is dangerous.
EHRA proposal for a universal NOAC anticoagulation card

Card can be downloaded in a printer-ready form or in a ppt format that can be configured to the local language from www.NOACforAF.eu
Need for structured follow-up

- All NOACs are anticoagulants and hence can cause serious bleeding.
- All NOACs have some drug-drug interactions (DDIs).
- AF population is a fragile patient population.
- Patients should return for ongoing review according to a predetermined schedule.
- Follow-up can be undertaken by specialist or GP with experience in the field and/or appropriate secondary care physicians.
- Nurse co-ordinated AF clinics may be used. ¹

¹ Berti et al, Eur Heart J, 2013 (Epub ahead of print)
Suggested structured follow-up

Initiator of anticoagulant treatment:
- Sets indication for anticoagulation;
- Makes choice of anticoagulant;
- Decides on need of proton pump inhibitor;
- Baseline hemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organises follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.

First FU: 1 month

Follow-up: GP; anticoagulant clinic; initiator of therapy; ...

Checks:
1. Compliance (patient should bring remaining pills);
2. Thrombo-embolic events;
3. Bleeding events;
4. Other side effects;
5. Co-medications and over-the-counter drugs.
6. Need for blood sampling?

1 m?
3 m
6 m?

In case of problems: contacts initiator of treatment.

Else: fills out anticoagulation card and sets date/place for next follow-up.

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# Checklist during follow-up of AF patients on NOACs

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance</td>
<td>Each visit</td>
<td>Inspect remaining medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress importance of compliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inform about compliance aids</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>Each visit</td>
<td>Cerebral, systemic and pulmonary circulation</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Each visit</td>
<td>“Nuisance” bleeding – prevention possible?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleeding with risk or impact on QoL – prevention possible? Need to revise dose?</td>
</tr>
<tr>
<td>Side effects</td>
<td>Each visit</td>
<td>Continuation? Temporary cessation with bridging? Change of anticoagulant drug?</td>
</tr>
<tr>
<td>Co-medications</td>
<td>Each visit</td>
<td>Prescription or over-the-counter drugs?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Even temporary use can be risky</td>
</tr>
<tr>
<td>Blood sampling</td>
<td>Yearly</td>
<td>Haemoglobin, renal, liver function</td>
</tr>
<tr>
<td></td>
<td>6-monthly</td>
<td>Renal function if CrCl 30-60 ml/min or if on dabigatran and aged &gt;75 years or fragile</td>
</tr>
<tr>
<td></td>
<td>3-monthly</td>
<td>If CrCl 15-30 ml/min</td>
</tr>
<tr>
<td></td>
<td>on indication</td>
<td>If intercurring condition may impact renal or hepatic function.</td>
</tr>
</tbody>
</table>

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Follow-up: considerations

- Renal function: impaired renal function increases plasma levels and hence anticoagulant effect of all NOACs, especially dabigatran. Dose reduction may be indicated.

- Minor bleeding: most is temporary and classified as ‘nuisance’. Discontinuation or dose reduction should not be considered unless frequent and impacting on patient’s QoL.
2. How to measure the anticoagulant effect of NOACs

Routine monitoring of coagulation not required, but quantitative assessment of drug exposure may be needed in emergency situations:

- serious bleeding and thrombotic events
- urgent surgery
- renal or hepatic insufficiency
- potential DDI
- suspected overdosing
Measuring the anticoagulant effect of NOACs

- Important to know exactly when NOAC was administered relative to time of blood sampling. Maximum effect at maximum plasma concentration (~3h after administration).

- Activated thromboplastin time (aPTT): qualitative assessment of dabigatran, but sensitivity varies.

- Diluted thrombin time (DTT): Hemoclot® suitable for quantitative assessment of dabigatran but no data on cut off below which surgery is safe.

- Anti-FXa chromogenic assays: commercially available for quantitative assessment, but no data to associate level with bleeding or thromboembolism risk.
Measuring the anticoagulant effect of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma peak</td>
<td>2h after ingestion</td>
<td>1-4h post ingestion</td>
<td>1-2h after ingestion</td>
<td>2-4h after ingestion</td>
</tr>
<tr>
<td>Plasma trough</td>
<td>12-24h after ingestion</td>
<td>12-24h after ingestion</td>
<td>12-24h after ingestion</td>
<td>16-24h after ingestion</td>
</tr>
<tr>
<td>PT</td>
<td>cannot be used</td>
<td>cannot be used</td>
<td>prolonged but no known relation with bleeding risk</td>
<td>prolonged: may indicate excess bleeding risk but local calibration required</td>
</tr>
<tr>
<td>INR</td>
<td>cannot be used</td>
<td>cannot be used</td>
<td>cannot be used</td>
<td>cannot be used</td>
</tr>
<tr>
<td>aPTT</td>
<td>at trough &gt;2x ULN suggests excess bleeding risk</td>
<td>cannot be used</td>
<td>prolonged but no known relation with bleeding risk</td>
<td>cannot be used</td>
</tr>
<tr>
<td>dTT</td>
<td>At trough &gt;200ng/ml ≥ 65s: excess bleeding risk</td>
<td>cannot be used</td>
<td>cannot be used</td>
<td>cannot be used</td>
</tr>
<tr>
<td>Anti-FXa assays</td>
<td>n/a</td>
<td>no data yet</td>
<td>quantitative; no data on threshold values for bleeding or thrombosis</td>
<td>quantitative; no data on threshold values for bleeding or thrombosis</td>
</tr>
<tr>
<td>Ecarin clotting time</td>
<td>at trough &gt;2x ULN: excess bleeding risk</td>
<td>not affected; cannot be used</td>
<td>not affected; cannot be used</td>
<td>not affected; cannot be used</td>
</tr>
</tbody>
</table>
Curvilinear relationship between aPTT and dabigatran plasma levels

Van Ryn et al Thrombosis and haemostats 2010;103:1126-7

www.escardio.org/EHRA
Relation between PT and FXa inhibitor (rivaroxaban) plasma levels

Douxfils et al Thromb Res. 2012;130:956-66

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3. Drug-drug interactions and pharmacokinetics of NOACs

Absorption and metabolism of NOACs

Dabigatran
- Esterase-mediated hydrolysis
- Bioavailability 3–7%
- $t_{1/2} = 12-17h$
- $\sim 20\%$

Rivaroxaban
- Bioavailability: 66% (without food)
- $>80\%$ (with food)
- $t_{1/2} = 5-9h$ (young)
- $11-13h$ (elderly)
- $\sim 65\%$
- $\sim 35\%$

Apixaban
- Bioavailability 50%
- $t_{1/2} = 12h$
- $\sim 73\%$

Edoxaban
- Bioavailability 62%
- $t_{1/2} = 9-11h$
- $\sim 50\%$

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# Absorption and metabolism of NOAC

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban *</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>3-7%</td>
<td>50%</td>
<td>62%</td>
<td>66% (w/o food) ~100% with food</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>Clearance:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-renal/renal of adsorbed dose if normal renal function</td>
<td>20%/80%</td>
<td>73%/27%</td>
<td>50%/50%</td>
<td>65%/35%</td>
</tr>
<tr>
<td><strong>Liver metabolism:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>no</td>
<td>yes (elimination; minor CYP3A4)</td>
<td>minimal (&lt;4% of elimination)</td>
<td>yes (elimination)</td>
</tr>
<tr>
<td><strong>Absorption with food</strong></td>
<td>no effect</td>
<td>no effect</td>
<td>6-22% more</td>
<td>+39%</td>
</tr>
<tr>
<td><strong>Intake with food?</strong></td>
<td>no</td>
<td>no</td>
<td>no official recommendation yet</td>
<td>mandatory</td>
</tr>
<tr>
<td><strong>Absorption with H2B/PPI</strong></td>
<td>plasma level -12 to -30%</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td><strong>Asian ethnicity</strong></td>
<td>plasma level +25%</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td><strong>GI tolerability</strong></td>
<td>dyspepsia 5-10%</td>
<td>no problem</td>
<td>no problem</td>
<td>no problem</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>12-17h</td>
<td>12h</td>
<td>9-11h</td>
<td>5-9h (young)/11-13h (elderly)</td>
</tr>
</tbody>
</table>

* not approved yet

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Mechanisms underlying DDIs in NOACs

• P-glycoprotein transporter involved in absorption and renal clearance – plasma levels may be affected by P-gp inducers or inhibitors\(^1\)

• Cytochrome P450 CYP3A4 involved in hepatic clearance of rivaroxaban and apixaban – plasma levels may be affected by CYP3A4 inducers of inhibitors\(^2\)

Action to be taken in case of DDIs

Three levels of alert:

• Red – contraindicated/not recommended for use

• Orange – adapt NOAC dose
  – dabigatran: 150 mg to 110 mg BID
  – rivaroxaban: 20 mg to 15 mg QD
  – apixaban: 5 mg to 2.5 mg BID

• Yellow – consider dose reduction if two concomitant yellow interactions

• Where no data available, NOACs not recommended yet
### Possible drug-drug interactions – Effect on NOAC plasma levels part 1

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Dabigatran Effect</th>
<th>Apixaban Effect</th>
<th>Edoxaban Effect</th>
<th>Rivaroxaban Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>+18%</td>
<td></td>
<td></td>
<td>no effect</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>no effect</td>
<td></td>
<td></td>
<td>no effect</td>
</tr>
<tr>
<td><strong>Verapamil</strong></td>
<td>+12–180%</td>
<td>+53% (slow release)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diltiazem</strong></td>
<td>no effect</td>
<td>+40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quinidine</strong></td>
<td>+50%</td>
<td></td>
<td>+80%</td>
<td>+50%</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>+12–60%</td>
<td></td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td><strong>Dronedarone</strong></td>
<td>+70–100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ketoconazole; itraconazole; voriconazole; posaconazole;</strong></td>
<td>+140–150%</td>
<td>+100%</td>
<td>up to +160%</td>
<td></td>
</tr>
</tbody>
</table>

**Key**
- Red – contraindicated
- Orange – reduce dose
- Yellow – consider dose reduction if another yellow factor present
- Hatching – no data available
- Recommendation made from pharmacokinetic considerations

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### Possible drug-drug interactions – Effect on NOAC plasma levels part 2

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole CYP3A4</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>+42%</td>
</tr>
<tr>
<td>Cyclosporin; tacrolimus P-gp</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>+50%</td>
</tr>
<tr>
<td>Clarithromycin; erythromycin P-gp/CYP3A4</td>
<td>+15–20%</td>
<td>no data</td>
<td>no data</td>
<td>+30–54%</td>
</tr>
<tr>
<td>HIV protease inhibitors P-gp and BCRP/ CYP3A4</td>
<td>no data</td>
<td>strong increase</td>
<td>no data</td>
<td>up to +153%</td>
</tr>
<tr>
<td>Rifampicin; St John’s wort; carbamezepine; phenytoin; phenobarbital P-gp and BCRP/ CYP3A4/CYP2J2</td>
<td>-66%</td>
<td>-54%</td>
<td>-35%</td>
<td>up to -50%</td>
</tr>
<tr>
<td>Antacids GI absorption</td>
<td>-12-30%</td>
<td>no data</td>
<td>no effect</td>
<td>no effect</td>
</tr>
</tbody>
</table>

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations
Factors associated with raised plasma levels of NOACs part 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged ≥ 80 years</td>
<td>Increased</td>
<td></td>
<td></td>
<td>no data</td>
</tr>
<tr>
<td>Aged ≥ 75 years</td>
<td>Increased</td>
<td></td>
<td></td>
<td>no data</td>
</tr>
<tr>
<td>Weight ≤ 60 kg</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs
Systemic steroid therapy
Other anticoagulants
Recent surgery on critical organ (brain, eye)
Thrombocytopenia (e.g. chemotherapy)
HAS-BLED ≥ 3

Other increased bleeding risk

Orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

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## 4. Switching between anticoagulant regimens

<table>
<thead>
<tr>
<th>Transition</th>
<th>INR &lt;2.0: immediate</th>
<th>INR 2.0–2.5: immediate or next day</th>
<th>INR &gt;2.5: use INR and VKA half-life to estimate time to INR &lt;2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA to NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral anticoagulant to NOAC:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous unfractioned heparin (UFH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low molecular weight heparin (LMWH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start once UFH discontinued ($t_{1/2}=2h$). May be longer in patients with renal impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start when next dose would have been given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC to VKA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer concomitantly until INR in appropriate range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure INR just before next intake of NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-test 24h after last dose of NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor INR in first month until stable values (2.0–3.0) achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC to parenteral anticoagulant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate when next dose of NOAC is due</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC to NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate when next dose is due except where higher plasma concentrations expected (e.g. renal impairment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin or clopidogrel to NOAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch immediately, unless combination therapy needed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. Ensuring compliance with NOAC intake

Important – anticoagulant effect drops rapidly after 12-24 h

• QD better adherence than BID for cardiovascular drugs in general, but no data on superior dosing scheme for NOAC in clinical practice.

• Patient education crucial: leaflets and instruction at initiation, patient safety card, group sessions.

• Involve family members.

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Ensuring compliance with NOAC intake

- Nurse-co-ordinated AF centres to focus on compliance?
- Technological aids – medication boxes, smartphone apps.
- INR monitoring not needed/not useful.
- Involve pharmacy?
- If low compliance despite these, consider VKAs.
### 6. How to deal with dosing errors

<table>
<thead>
<tr>
<th>Category</th>
<th>BID:</th>
<th>QD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed dose:</td>
<td>take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose.</td>
<td>take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.</td>
</tr>
<tr>
<td>Double dose:</td>
<td>skip next planned dose and restart BID after 24 h.</td>
<td>continue normal regimen.</td>
</tr>
<tr>
<td>Uncertainty about intake:</td>
<td>continue normal regimen.</td>
<td>take another dose then continue normal regimen.</td>
</tr>
<tr>
<td>Overdose:</td>
<td>Hospitalization advised.</td>
<td></td>
</tr>
</tbody>
</table>
7. Patients with chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥ 60 ml/min</td>
<td>~ 14 h&lt;sup&gt;1&lt;/sup&gt;</td>
<td>no data</td>
<td>~ 8.6 h&lt;sup&gt;2&lt;/sup&gt;</td>
<td>~ 8.5 h&lt;sup&gt;3&lt;/sup&gt; (+44%)</td>
</tr>
<tr>
<td>CKD Stage I &amp; II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 30–60 ml/min</td>
<td>~ 18 h&lt;sup&gt;1&lt;/sup&gt;</td>
<td>no data</td>
<td>~ 9.4 h&lt;sup&gt;2&lt;/sup&gt;</td>
<td>~ 9 h&lt;sup&gt;3&lt;/sup&gt; (+52%)</td>
</tr>
<tr>
<td>CKD Stage III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 15–30 ml/min</td>
<td>~ 28 h&lt;sup&gt;1&lt;/sup&gt;</td>
<td>no data</td>
<td>~ 16.9 h&lt;sup&gt;2&lt;/sup&gt;</td>
<td>~ 9.5 h&lt;sup&gt;3&lt;/sup&gt; (+64%)</td>
</tr>
<tr>
<td>CKD Stage IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≤ 15 ml/min</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>CKD Stage V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Stangier et al, Clinical pharmacokinetics 2010;49:259-68

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### NOACs in renal dysfunction – Approved European labels

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of absorbed dose</td>
<td>80%</td>
<td>27%</td>
<td>50%(^1)</td>
<td>35%</td>
</tr>
<tr>
<td>renally excreted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bio-availability</td>
<td>3-7%</td>
<td>50%</td>
<td>62%(^2)</td>
<td>66% without food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>~ 100% with food</td>
</tr>
<tr>
<td>% of administered dose</td>
<td>4%</td>
<td>14%</td>
<td>37%</td>
<td>33%</td>
</tr>
<tr>
<td>renally excreted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved for CrCl</td>
<td>≥30 ml/min</td>
<td>≥15 ml/min</td>
<td>not available</td>
<td>≥15 ml/min</td>
</tr>
<tr>
<td>Label dosing</td>
<td>CrCl ≥15 ml/min, no adjustment (i.e. 150 mg BID)</td>
<td>Serum creatinine ≥1.5 ml/dl, no adjustment (i.e. 5 mg BID)</td>
<td>CrCl ≥ 50 ml/min, no adjustment (i.e. 20 mg QD)</td>
<td>recommendation</td>
</tr>
</tbody>
</table>


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## NOACs in renal dysfunction – Practical recommendations for dosing in chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th><strong>Dabigatran</strong></th>
<th><strong>Apixaban</strong></th>
<th><strong>Edoxaban</strong></th>
<th><strong>Rivaroxaban</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>When CrCl 30-49 ml/min, 150 mg BID is possible (SmPC) but 110 mg BID if ‘high risk of bleeding’ (SmPC) or ‘recommended’ (GL update)¹</td>
<td>**Note: 75 mg BID approved in US only **</td>
<td>CrCl 15-29 ml/min: 2.5 mg BID is possible Serum creatinine ≥ 1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) or with other yellow’ factor: 2.5 mg BID</td>
<td>not available</td>
<td>15 mg OD when CrCl 15-49 ml/min</td>
</tr>
<tr>
<td>Note: 75 mg BID approved in US only **</td>
<td>-if CrCl 15-30 ml/min - if CrCl 30-49 ml/min - and other orange factor (e.g. verapamil)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No EMA approval yet. Needs update after finalisation of SmPC. ** No EMA indication. FDA recommendation based on pharmacokinetics. Carefully consider benefits and risks of this approach. Note that 75 mg capsules are not available in Europe for AF indication.

NOACs in chronic kidney disease – Clinical evidence

• CKD a risk factor for both thrombo-embolic events and bleeding\(^1,2\)
• CrCl <60 ml/min may predict increased stroke and systemic embolism\(^3\)
• In Phase III trials, similar AUCs for reduced doses in patients with decreased renal function as for higher dose in patients with normal renal function\(^4\)
• Rivaroxaban approved for people with CKD stage IV, with lower dose regimen, but should be used with caution: no trial data available in patients with CrCl 15-30 ml/min
• Low dose dabigatran (75 mg BID) approved by FDA but not EMA for patients with severe renal insufficiency

NOACs in chronic kidney disease – Practical suggestions

- CKD should be considered an additional risk factor for stroke in AF but CKD also increases bleeding risk
- NOACs are a reasonable choice for anticoagulant therapy in AF patients with mild or moderate CKD
- NOACs similar benefit/risk ratio to VKAs with rivaroxaban (15 mg QD) in renal impairment (CrCl <50 ml/min).\(^1\)
  With apixaban, there may be a lower relative bleeding risk\(^2\)

1. Fox et al, Eur Heart J 2011;32:2387-94
NOACs in chronic kidney disease – Practical suggestions

- Dabigatran may not be first choice as primarily cleared renally but may be used in stable patients.
- FXa inhibitors have 25-50% renal clearance therefore may be preferred.
- Consider dose reductions in patients with CrCl <50 ml/min: apixaban 2.5 mg BID,¹ rivaroxaban 15 mg/day²
- Avoid NOACs in AF patients on haemodialysis: consider VKAs

1. Fox et al, Eur Heart J 2011;32:2387-94

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NOACs in chronic kidney disease – Practical suggestions

- Monitor renal function regularly and adapt the dose accordingly
- Monitor renal function at the following intervals:

<table>
<thead>
<tr>
<th>Interval</th>
<th>Stage/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly</td>
<td>stage I-II (CrCl ≥ 60 ml/min)</td>
</tr>
<tr>
<td>6-monthly</td>
<td>stage III, elderly (&gt;75 yrs) or frail patients on dabigatran (CrCl 30–60 ml/min)</td>
</tr>
<tr>
<td>3-monthly</td>
<td>stage IV (CrCl ≤ 30 ml/min)</td>
</tr>
</tbody>
</table>
8. What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding

- Acute recent ingestion of overdose: activated charcoal to reduce absorption (standard dosing scheme for adults of 30 to 50 g).
- Consider coagulation tests to assess possible bleeding risk.
- In absence of bleeding, wait-and see approach.
9. Management of bleeding complications
Possible measures to take in case of bleeding
part 1

Non life-threatening

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>FXa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inquire last intake + dosing regimen</td>
<td>Inquire last intake + dosing regimen</td>
</tr>
<tr>
<td>Estimate normalization of haemostasis</td>
<td>Normalisation of haemostasis: ±24h</td>
</tr>
<tr>
<td>Normal renal function: ±24h</td>
<td></td>
</tr>
<tr>
<td>CrCl 50-80 ml/min: 24-36h</td>
<td></td>
</tr>
<tr>
<td>CrCl 30-50 ml/min: 36-48h</td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;30 ml/min: ≥48h</td>
<td></td>
</tr>
<tr>
<td>Maintain diuresis</td>
<td>Local haemostatic measures</td>
</tr>
<tr>
<td>Local haemostatic measures</td>
<td>Fluid replacement (colloids if needed)</td>
</tr>
<tr>
<td>Fluid replacement (colloids if needed)</td>
<td></td>
</tr>
</tbody>
</table>
Possible measures to take in case of bleeding part 2

Non life-threatening

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>FXa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC substitution if necessary</td>
<td>RBC substitution if necessary</td>
</tr>
<tr>
<td>Platelet substitution (in case of thrombocytopenia ≤ 60 x 10⁹ /L or thrombopathy)</td>
<td>Platelet substitution (in case of thrombocytopenia ≤ 60 x 10⁹ /L or thrombopathy)</td>
</tr>
<tr>
<td>Fresh frozen plasma as plasma expander (not as reversal agent)</td>
<td>Fresh frozen plasma as plasma expander (not as reversal agent)</td>
</tr>
<tr>
<td>Tranexamic acid can be considered as adjuvans</td>
<td>Tranexamic acid can be considered as adjuvans</td>
</tr>
<tr>
<td>Desmopressin can be considered in special cases (coagulopathy or thrombopathy)</td>
<td>Desmopressin can be considered in special cases (coagulopathy or thrombopathy)</td>
</tr>
<tr>
<td>Consider dialysis (primary evidence: - 65% after 4h)</td>
<td></td>
</tr>
<tr>
<td>Charcoal haemoperfusion not recommended (no data)</td>
<td></td>
</tr>
</tbody>
</table>
## Possible measures to take in case of bleeding

**part 3**

### Life-threatening

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>FXa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the above</td>
<td>All of the above</td>
</tr>
<tr>
<td>Prothrombin complex concentrate (PCC) 25 U/g (may be repeated once or twice but no clinical evidence)</td>
<td>Prothrombin complex concentrate 25 U/kg (may be repeated once or twice but no clinical evidence)</td>
</tr>
<tr>
<td>Activated PCC 50IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available</td>
<td>Activated PCC 50IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available</td>
</tr>
<tr>
<td>Activated factor VII (rFVIIa; 90μg/kg); no data about additional benefit + expensive (only animal evidence)</td>
<td>Activated factor VII (rFVIIa; 90μg/kg); no data about additional benefit + expensive (only animal evidence)</td>
</tr>
</tbody>
</table>
Possible measures to take in case of bleeding

**Bleeding while using a NOAC**

- **Mild bleeding**
  - Delay or discontinue next dose
  - Reconsider concomitant medication

- **Moderate severe bleeding**
  - Supportive measures:
    - mechanical compression
    - surgical hemostasis
    - fluid replacement (colloids if needed)
    - RBC substitution if needed
    - fresh frozen plasma (as plasma expander)
    - platelet substitution (if platelet count ≤60x10⁶/L)

  For dabigatran:
  - maintain adequate diuresis
  - consider hemodialysis
  - ((charcoal hemoperfusion?: await more data))

- **Life-threatening bleeding**
  - Consider:
    - PCC (e.g. CoFact®) 25 U/kg; repeat 1x/2x if indicated
    - aPCC (Feiba®) 50IE/kg; max 200 IE/kg/day
    - ((rFVIIa (NovoSeven®) 90µ/kg no data about additional benefit))


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10. Patients undergoing a planned surgical intervention or ablation

Classification of surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulant

Perform procedures at ‘through’ levels of NOAC. Consider scheduling intervention 18-24 h after last intake and then restart 6 h later (i.e. skipping 1 dose with BID NOAC)

- Dental interventions
  - Extraction of 1 to 3 teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision, small dermatological excision)
Classification of surgical interventions according to bleeding risk

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endoscopy with biopsy</td>
<td>• Complex left-sided ablation: pulmonary vein isolation, VT ablation</td>
</tr>
<tr>
<td>• Prostate or bladder biopsy</td>
<td>• Spinal or epidural anaesthesia; lumbar diagnostic puncture</td>
</tr>
<tr>
<td>• Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left sided ablation via single transseptal puncture)</td>
<td>• Thoracic surgery</td>
</tr>
<tr>
<td>• Angiography</td>
<td>• Abdominal surgery</td>
</tr>
<tr>
<td>• Pacemaker or ICD implantation (unless complex anatomical setting e.g. congenital heart disease)</td>
<td>• Major orthopedic surgery</td>
</tr>
<tr>
<td></td>
<td>• Liver biopsy</td>
</tr>
<tr>
<td></td>
<td>• Transurethral prostate resection</td>
</tr>
<tr>
<td></td>
<td>• Kidney biopsy</td>
</tr>
</tbody>
</table>
When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban *</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CrCl ≥80 ml/min</strong></td>
<td>Low risk: ≥24h</td>
<td>High risk: ≥48h</td>
<td>Low risk: ≥24h</td>
<td>High risk: ≥48h</td>
</tr>
<tr>
<td><strong>CrCl 50–80 ml/min</strong></td>
<td>Low risk: ≥36h</td>
<td>High risk: ≥72h</td>
<td>Low risk: ≥24h</td>
<td>High risk: ≥48h</td>
</tr>
<tr>
<td><strong>CrCl 30–50 ml/min §</strong></td>
<td>Low risk: ≥48h</td>
<td>High risk: ≥96h</td>
<td>Low risk: ≥24h</td>
<td>High risk: ≥48h</td>
</tr>
<tr>
<td><strong>CrCl 15–30 ml/min §</strong></td>
<td>not indicated</td>
<td>not indicated</td>
<td>Low risk: ≥36h</td>
<td>High risk: ≥48h</td>
</tr>
<tr>
<td><strong>CrCl &lt;15 ml/min</strong></td>
<td>no official indication for use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*no EMA approval yet.; Low risk: surgery with low risk of bleeding. High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).
When to restart NOACs after a planned surgical intervention

<table>
<thead>
<tr>
<th>Procedures with immediate and complete haemostasis:</th>
<th>Resume 6–8 h after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atraumatic spinal/epidural anethesia</td>
<td></td>
</tr>
<tr>
<td>Clean lumbar puncture</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedures associated with immobilization:</th>
<th>Initiate reduced venous or intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures with post-operative risk of bleeding:</td>
<td>Restart NOACs 48–72h after surgery upon complete haemostasis</td>
</tr>
<tr>
<td></td>
<td>Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery</td>
</tr>
</tbody>
</table>

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Recommendations for stopping and starting NOACs after AF ablation procedures

- Limited available data. 1-5
- Recommend strategy of bridging (with well-timed preoperative discontinuation, as above: slide 40) and restarting of NOACs.
- A too aggressively shortened periprocedural cessation of NOACs and/or no bridging may be less safe when compared to continued VKA administration and ablation under an INR between 2.0 and 3.0, both concerning bleeding and cardioembolic complications.

2. Kaseno et al, Circ J 2012; 76:2337-42
5. Kim et al, Heart Rhythm, 2013 (ePub ahead of print)
11. Patients undergoing an urgent surgical intervention

- Discontinue NOAC.
- Try to defer surgery at least 12 h and ideally 24 h after last dose.
- Urgent surgery associated with much higher rates of bleeding than elective procedures, but lower than VKA-treated patients.¹
- Coagulation tests can be considered (classical test or specific tests) but strategy based on these results has never been evaluated. Therefore such strategy cannot be recommended and should not be used routinely.

¹ Healey et al, Circulation 2012:126;343-8
12. Patients with AF and coronary heart disease
Clinical evidence part 1

- AF with ST-elevation (STE) or non ST-elevation (NSTE) ACS is associated with higher mortality rates. ¹
- Thrombotic vs bleeding risk in published trials and cohorts influenced by comorbidities and local practice.
- Triple therapy with VKA doubles risk of bleeding complications compared with clopidogrel + VKA. ²,³
- Triple therapy with double antiplatelet drug therapy (DAPT) and NOACs at least doubles bleeding risk after ACS. ⁴
- Data from RE-LY trial suggests that the advantages of NOAC over VKA in dual or triple therapy are preserved, but no comparative trial data to recommend one over the other. ⁵


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Patients with AF and coronary heart disease
Clinical evidence part 2

• No Phase III trial data available for evaluation of NOACs in patients with recent ACS.

• In a meta-analysis of dabigatran trials, small but significant increased rate of MIs with dabigatran vs VKA (OR 1.33, 95% CI 1.03–1.71, p=0.03) but without impact on overall net clinical survival benefit \(^1,^2\) No excess MI observed in AF trials assessing FXa inhibitors.

• After ACS, DAPT with apixaban increases major bleeding risk. \(^3\)

• Low-dose rivaroxaban with DAPT improves ischemic outcome after ACS but increased major bleeding risk.

1. Uchino et al, Arch Intern Med 2012;172:397-402

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Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 1

- Temporarily discontinue NOACs upon presentation
- Initiate DAPT therapy unless frail with high bleeding risk
- Administer low-dose aspirin (150–300 mg loading; 75–100 mg later) on admission, preferably combined with ADP receptor inhibitor (ticagrelor or prasugrel preferred over clopidogrel)
- Initiate paraenteral anticoagulation (fondaparinux preferred)
Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 2

In case of STEMI:

use primary PCI (radial approach) over fibrinolysis
• avoid UFH or enoxaparin until NOAC effect disappeared

In case of NSTE-ACS:

if not urgent, delay coronary angiography until waning of NOAC effect
• peri-procedural anticoagulation (UFH or bivalirudin preferred)


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Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 3

In case of PCI:

- use radial approach
- if indicated, balloon angioplasty without stenting
- use bare metal stents
- use additional paraenteral anticoagulation
- periprocedural bivalirudin preferred. Discontinue immediately after PCI
- avoid glycoprotein IIb/IIIa inhibitors unless bail-out situations
Scenario 1. Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) part 4

- In patients requiring revascularization, bypass surgery may be preferred in selected patients.

- When restarting NOAC consider dose reduction according risk and aim for shortest necessary duration of dual/triple therapy.

- Newer platelet inhibitors prasugrel and ticagrelor have not been evaluated for NOACs. Recommend awaiting further data before combining these with NOACs.
Scenario 2. Recommendations concerning new onset AF in patients with a recent (<1y) ACS part 1

- In patients with low atherothrombotic risk, consider VKAs in monotherapy after 1-3 months (6 months in case of recent DES), especially where bleeding risk elevated (HAS-BLED ≥3).

- In patients with high GRACE score (> 118), use additional single antiplatelet therapy (clopidogrel preferred) in the first 6 to 12 months after the acute event.

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Scenario 2. Recommendations concerning new onset AF in patients with a recent (<1y) ACS part 2

- If NOAC indicated, consider FXa inhibitor (small and insignificant increased risk of MI for dabigatran, but weigh against clinical benefit).

- If dabigatran indicated, consider low dose (110 mg BID), in combination with low-dose aspirin or with clopidogrel.

- Ultra-low dose rivaroxaban in combination with DAPT has not been evaluated in this setting and is not currently recommended.
Scenario 3. Recommendations concerning new onset AF in patients with a remote (>1 year ACS)

- Anticoagulation without additional antiplatelet agents is sufficient for most AF patients with stable CAD.
- Advantages of NOACs over VKAs likely to be preserved: NOACs may be safe and effective alternatives to VKAs. \(^\text{1}\)
- No preference given to any of NOACs.
- If using dabigatran, consider lower dose (110 mg BID) plus low-dose aspirin (clopidogrel in case of allergy to aspirin). \(^\text{2}\)

13. Cardioversion in a NOAC treated patient

- In patients with AF >48h duration undergoing cardioversion, oral anticoagulants should have been given for at least 3 weeks before cardioversion.
- Continuous oral anticoagulation is mandatory for 4 weeks following cardioversion.
- Clinical trial data show no significant additional risk in patients treated with NOACs vs. VKAs. ¹
- If NOAC compliance can be reliably confirmed, cardioversion should be safe.
- If doubt about compliance, consider prior TEE. ²

¹ Nagarakanti et al Circulation 2011;123:131-6;
² Piccini et al Circulation 2012;126:A19281
14. Patients presenting with acute stroke while on NOACs

Acute haemorrhagic stroke

- Discontinue NOACs.
- Limited data to support use of aspecific procoagulants e.g. PCC, aPCC and aFVII.
- Use PCC or fresh frozen plasma as discussed in slides about measures in case of major bleeding.
- Same poor prognosis as for warfarin.¹

¹ Hart et al. Stroke 2012;43:1511-7

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Patients presenting with acute stroke while on NOACs

Acute ischaemic stroke

- Assess the time window since last intake of NOAC: thrombolytic therapy is associated with increased bleeding risk within 48h of last NOAC dose.
- In case of uncertainty regarding last dose, prolonged aPTT (dabigatran) or PT (FXa inhibitors) indicates that thrombolysis should not be given.
- If NOACs have been given within 48h and coagulation tests not available or abnormal, consider recanalization of occluded vessels.

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Stroke patients –
Management of post-acute phase

Haemorrhagic stroke

• If cardioembolic risk high and risk of new haemorrhage low, restart NOACs 10-14 days after intracerebral haemorrhage.
• For patients with low cardioembolic risk and high bleeding risk, carefully consider reinintiation of NOACs: contraindicated unless bleeding risk has been reversed.
• Consider non pharmacological strategies instead of NOACs (e.g. ablation or occlusion of the atrial appendage).
• Mechanical thrombectomy without thrombolysis: no restrictions.
Stroke patients – Management of post-acute phase

Ischaemic stroke

- If infarct size not expected to increase risk of secondary intracerebral bleeding, re-initiate:
  - in patients with TIA after 1 day
  - small, non-disabling infarct after 3 days
  - large infarcts not before 2 weeks

TIA of cardioembolic origin

- (Re)start NOACs as soon as possible.
- Bridging with LMWH not required.
- In AF patients not suitable for VKAs, apixaban is superior to aspirin in stroke prevention.¹

¹ Connolly et al, N Engl J Med 2011;364:808-17
Stroke patients – Management of post-acute phase

Ischemic stroke of cardioembolic origin

- Initiation of NAOCs depends on infarct size and risk of new embolic stroke.
- Bridging with LMHW not required.
- Aspirin is not useful in secondary stroke prevention.

Patients with AF and significant carotid stenosis

- Carotid endarterectomy and not stenting recommended to avoid triple therapy.
15. NOACs vs VKAs in AF patients with a malignancy

- Patients with malignancies are at increased risk for thromboembolic events: tumours may secrete prothrombotic factors or induce inflammatory responses.
- Cancer therapy inflicts bleeding risks through surgery, tissue damage (irradiation) or myelosuppression.
- Many malignancies are associated with increased risk of mucosal bleeding.
- Chemotherapy causes myelosuppression (leucopenia/ reduced platelet count). This also reduces red blood cells and therefore reduces safety margin in a bleeding event.
NOACs in patients with cancer – Practical suggestions part 1

- Multidisciplinary care by cardiologist and oncologist.
- When new anticoagulant initiation is needed, consider VKA over NOACs: more clinical experience and reversal options, although INR is difficult to manage.
- Malignancy in patients with AF increases stroke risk.
- If already on stable NOAC treatment: continue unless contraindications, i.e. switch to VKA not mandatory.
NOACs in patients with cancer – Practical suggestions part 2

- No additional anticoagulant therapy (e.g. LMHW) is needed if NOACs are used.
- In patients receiving moderately myelosuppressive therapies, NOACs may be continued.
- In patients undergoing tumour surgery, same principles apply as in elective surgery.
- Consider therapy-induced changes in organ function and adapt dose if indicated.
NOACs in patients with cancer – Practical suggestions part 3

- In patients undergoing myelosuppressive chemotherapy or radiation therapy, consider temporary dose reduction or cessation of NOACs.
- Monitor blood counts, bleeding signs and liver and renal function.
- Consider gastric protection with PPI or H2 blockers in all patients treated with NOACs.
- Patients on NOACs should be instructed to monitor signs of bleeding (petechiae, haemoptysis, black stools) and to contact therapy centre if these develop.
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