Comparison of oral anticoagulants
Information for prescribers
March 2014

Key factors influencing anticoagulant choice

- **Licensing**: all NOACs are licensed for prevention of stroke in non-valvular atrial fibrillation plus at least one additional risk factor. Warfarin is licensed for use without additional risk factors.
- **NICE Guidance and Patient choice**: The decision about whether to start treatment with any NOAC should be made after an informed discussion between the clinician and the person about the risks and benefits of the NOAC compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in light of their level of international normalised ratio (INR) control.
- **Compliance**: NOACs are not a safe option in patients who are unsuitable for warfarin due to poor compliance or high bleeding risk. Patients prescribed NOACs should have an on-going review of treatment, preferably 3-monthly.¹
- **Risk of haemorrhage**: NOACs have a lower risk of catastrophic intra-cerebral haemorrhage but some (rivaroxaban and dabigatran 150mg) have a slightly higher risk of gastrointestinal haemorrhage.² ³
- **Reversal**: a major concern with the NOACs is the lack of an effective antidote. This is counterbalanced to some degree by the lower risk of severe haemorrhage reported within clinical trials when compared to warfarin.
- **Acute bleeding**: in the event of acute bleeding patients receiving a NOAC may require surgical haemostasis, fluid replacement, or blood products. These may also be appropriate for those receiving warfarin, in addition to vitamin K. Suggested approaches to the management of bleeding complications are outlined in the EHRA Practical guide on the use of NOACs.¹
- **Renal function**: dose reduction or cessation of the newer drugs may be required with reduced renal function.
- **Frequency of dosing**: dabigatran and apixaban require twice daily dosing, compared to once daily for rivaroxaban and warfarin
- **Extremes of BMI**: exposure to the NOACs varies by 20-30% at extremes of bodyweight (<50 kg or >100-120 kg).⁶ ⁷ Although no dose adjustment is required, this may be problematic given the difficulties in monitoring the therapeutic effects.
- **Specific indications**: where continuation of anticoagulation therapy up to and during a planned procedure (e.g. cardioversion, ablation, etc) would be considered advantageous, a NOAC may be appropriate where patient compliance can be reliably confirmed.¹

- **Monitored Dosage Systems**: neither warfarin nor dabigatran is suitable for use in a compliance aid.
- **Comparative costs**: each of the newer drugs has a considerably higher acquisition cost than warfarin. When the cost of INR monitoring is taken into account, warfarin is likely to remain the least expensive option up-front. Comparative cost-effectiveness is not clear.
- **Time in therapeutic range**: NOACs are likely to be beneficial in patients with INR regularly outside the therapeutic range despite good adherence to warfarin. Time in therapeutic range of ≥65% is considered good.⁹
- **INR testing**: INR testing with warfarin is time consuming, but provides an opportunity to monitor adherence and effectiveness.
- **Experience**: there is a lack of clinician experience of long term use of NOACs.
- **Acquisition Cost**: If a NOAC is preferred and where all other factors are equal the NOAC with the lowest acquisition cost should be chosen

Identification

- Patients anticoagulated with either warfarin or newer agents should carry a card identifying their medication and who to contact in case of emergency related to their anticoagulation. A sample EHRA card is available online.

When might warfarin be the preferred option?

- In patients with a history of GI problems warfarin is the preferred option due to a more favourable GI side effect profile, lower rates of GI haemorrhage compared with NOACs, and reversible nature.
- In patients with poor medication compliance, warfarin may be the preferred option as patients are reviewed regularly.
- Patients co-administered medication that may inhibit metabolism and potentiate bleeding risk with novel agents (e.g. azole anti fungals, ritonavir) can be more safely managed on warfarin as the INR may be adjusted accordingly. Patients will still need appropriate dose adjustment of warfarin on commencement or withdrawal of such therapy.

Active swapping from warfarin to novel agents:

- Where patients are established on warfarin with a stable INR there is little or no reason to actively swap over to novel agents. Patients who have warfarin-specific rather than anticoagulant-associated side effects (e.g. alopecia rather than bleeding) could be offered a novel agent.

This information is a summary to guide prescribers – for further information please consult individual SPCs at www.medicines.org.uk
<table>
<thead>
<tr>
<th>Warfarin⁵</th>
<th>Dabigatran⁶</th>
<th>Rivaroxaban⁵</th>
<th>Apixaban⁷</th>
</tr>
</thead>
</table>
| **Licensed indications** | Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation. | Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as:  
- prior stroke or transient ischemic attack  
- heart failure, NYHA class ≥ II  
- age ≥ 75 years  
- diabetes mellitus, or hypertension | Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as:  
- congestive heart failure  
- hypertension  
- age ≥ 75 years  
- diabetes mellitus  
- prior stroke or transient ischaemic attack | Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as:  
- prior stroke or transient ischaemic attack  
- age ≥ 75 years  
- hypertension  
- diabetes mellitus  
- symptomatic heart failure NYHA class ≥ II |
| **Locally-approved indications** | Approved in North of Tyne for use before cardioversion. | - | - |
| **NICE status** | N/A | TA 249 March 2012  
Recommended as an option for the prevention of stroke and systemic embolism within its licensed indication (as above)  
The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control. | TA 256 May 2012  
Recommended as an option for the prevention of stroke and systemic embolism within its licensed indication (as above)  
The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control. | TA 275 February 2013  
Recommended as an option for preventing stroke and systemic embolism within its marketing authorisation (as above)  
The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control. |
<p>| <strong>How does it work?</strong> | Warfarin has an effect on several steps of the clotting cascade using compounds made with vitamin K by the liver. | Acts as a direct thrombin (factor IIa) inhibitor. It is formulated as dabigatran etexilate, a pro-drug converted to dabigatran after administration. | Acts as a selective direct factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. | Inhibits free and clot-bound factor Xa, and prothrombinase activity. Prevents thrombin generation and thrombus development. No direct effects on platelet aggregation, but indirectly inhibits aggregation induced by thrombin. |</p>
<table>
<thead>
<tr>
<th><strong>Dose and Administration</strong></th>
<th><strong>Warfarin</strong>&lt;sup&gt;9&lt;/sup&gt;</th>
<th><strong>Dabigatran</strong>&lt;sup&gt;6&lt;/sup&gt;</th>
<th><strong>Rivaroxaban</strong>&lt;sup&gt;5&lt;/sup&gt;</th>
<th><strong>Apixaban</strong>&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable dose taken once daily dependent on INR</td>
<td>- Patients under 80 years: 150 mg twice daily</td>
<td>- 20 mg once daily</td>
<td>- 5 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>
|  | - Patients >80 years: 110 mg twice daily (due to the increased risk of bleeding in this population) | - 15mg once daily if CrCL 15-49 mL/min. Use with caution if CrCL is 15-49 mL/min due to an increased bleeding risk. | - Reduce to 2.5 mg twice daily in patients with two or more of the following characteristics:  
  - Age ≥80 years  
  - Body weight ≤60kg  
  - Serum creatinine ≥1.5mg/dL (133 micromoles/L)  
  - 2.5 mg twice daily in patients with CrCL 15-29 mL/min | |
|  | - Reduce to 110 mg twice daily in patients who are taking verapamil |  | | |
|  | - Consider 110 mg twice daily when the thromboembolic risk is low and the bleeding risk is high (e.g. CrCL 30-50 mL/min) or patients weigh <50kg. |  | | |
| **Monitoring** | Needs to be adjusted to the individual needs of the patient and therefore requires regular monitoring using blood tests. | Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as warfarin. Renal function should be assessed (calculate CrCL):  
  - in all patients before starting dabigatran and  
  - at least once a year<sup>6</sup>  
  A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran. | Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as warfarin. Renal function should be assessed (calculate CrCL):  
  - in all patients before starting rivaroxaban and  
  - at least once a year<sup>6</sup> | Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as warfarin. Renal function should be assessed (calculate CrCL):  
  - in all patients before starting apixaban and  
  - at least once a year<sup>6</sup> |
| **Efficacy** | A meta-analysis found for all strokes:<sup>10</sup>  
  Relative risk reduction: 64%, Absolute risk reduction: 2.7%. | Dabigatran 150 mg BD superior to warfarin for prevention of stroke and systemic embolism; dabigatran 110 mg non-inferior to warfarin.<sup>2</sup> | Rivaroxaban 15 mg or 20 mg OD non-inferior to warfarin for prevention of stroke and systemic embolism.<sup>3</sup> | Apixaban 2.5 mg or 5.0 mg BD superior to warfarin for the prevention of stroke or systemic embolism.<sup>4</sup> |
| **Time in therapeutic range (TTR)** | TTR of 65% or higher is considered to represent good control of warfarin therapy.<sup>8</sup>  
  Average TTR in the UK is 63%.<sup>1</sup> | Mean TTR in warfarin arm of pivotal trial: 64%<sup>2</sup> | Mean TTR in warfarin arm of pivotal trial: 55% (trial population with high risk for stroke)<sup>3</sup> | Mean TTR in warfarin arm of pivotal trial: 62%<sup>4</sup> |
<p>| <strong>Safety</strong> | Long-term safety based on 50 years use in clinical practice. | No information available on long-term safety. <strong>Contraindicated</strong> if CrCL &lt;30 mL/min | No information available on long-term safety. Dose reduction recommended where CrCL 15-49 mL/min. <strong>Not recommended</strong> if CrCL &lt;15 mL/min. | No information available on long-term safety. <strong>Not recommended</strong> if CrCL &lt;15 mL/min. |</p>
<table>
<thead>
<tr>
<th>Bleeding</th>
<th>Warfarin&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See respective agent for comparison</td>
<td><strong>Major bleeding:</strong> No difference between dabigatran 150 mg BD and warfarin. Less common with dabigatran 110 mg BD than warfarin. <strong>GI bleeding:</strong> More common with dabigatran 150 mg BD than warfarin (p&lt;0.0008). No difference between dabigatran 110 mg BD and warfarin. <strong>Intracranial bleeding:</strong> Less common with both doses of dabigatran than with warfarin (p&lt;0.001). Bleeding risk high in the frail and elderly, particularly with renal impairment and low body weight.</td>
<td><strong>Major bleeding:</strong> No difference between rivaroxaban and warfarin. <strong>GI bleeding:</strong> More common with rivaroxaban than warfarin (p&lt;0.001) <strong>Intracranial bleeding:</strong> less common with rivaroxaban than warfarin (p=0.02)</td>
<td><strong>Major bleeding:</strong> Less common with apixaban than warfarin (p&lt;0.001) <strong>GI bleeding:</strong> No difference between apixaban and warfarin <strong>Intracranial bleeding:</strong> Less common with apixaban than warfarin (p&lt;0.001) Under additional monitoring via MHRA Black Triangle scheme as of February 2014.</td>
</tr>
<tr>
<td>Side effects</td>
<td>Other side effects can include hair loss</td>
<td>Dyspepsia more frequent with both doses of dabigatran than warfarin. GI adverse events frequently led to drug discontinuation (7%, 6.5% and 3.9% in the dabigatran 150 mg, 110 mg and warfarin groups respectively). The rate of myocardial infarction (MI) was numerically, but not statistically significantly, higher with dabigatran in the pivotal trial (0.82% for 110 mg and 0.81% for 150 mg vs. 0.64% p=0.12).&lt;sup&gt;2,12,13&lt;/sup&gt; A meta-analysis combining 7 studies showed dabigatran was associated with a significantly higher risk of MI or ACS. The control group varied and included enoxaparin, warfarin and placebo.&lt;sup&gt;14&lt;/sup&gt;</td>
<td>There were no significant differences in the incidence of any adverse event other than bleeding in the pivotal rivaroxaban trial.&lt;sup&gt;3&lt;/sup&gt; The rate of MI was numerically, but not statistically significantly, lower in the rivaroxaban arm compared with warfarin.</td>
<td>There were no significant differences between warfarin and apixaban in the incidence of any adverse events in the pivotal apixaban trial.&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Effective and well known antidote, should a severe bleed occur whilst being treated</td>
<td>No antidote currently known. Patients with bleeding risk factors excluded from pivotal trial. Clearance can be increased with haemodialysis. Consequences of the lack of an effective reversal agent should not be underestimated. Prolonged bleeding has increased morbidity and possibly contributed to deaths.&lt;sup&gt;15&lt;/sup&gt;</td>
<td>No antidote currently known although prothrombin complex concentrate has been successful in showing normalisation of laboratory clotting parameters (prothrombin time and endogenous thrombin potential) in a small preliminary trial.&lt;sup&gt;16&lt;/sup&gt;</td>
<td>No antidote currently known.</td>
</tr>
<tr>
<td>Switching between anticoagulants</td>
<td>Warfarin&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Dabigatran&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Rivaroxaban&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Apixaban&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Switching to warfarin</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dosing of warfarin and NOAC should overlap until INR is &gt;2.0. This may take 5-10 days. Since NOACs can contribute to elevated INR, testing should be performed just before the next NOAC dose is due. Re-test 24h after the last dose of NOAC to ensure adequate anticoagulation.</td>
<td><strong>Switching from warfarin</strong>&lt;br&gt;SPC guidance: stop warfarin, start dabigatran when INR is &lt;2.0. <strong>EHRA guidance:</strong> initiate NOAC once INR is &lt;2.0. If INR is 2.0-2.5, start NOAC immediately or (better) next day. If INR &gt;2.5, estimate when INR is likely to drop below this threshold, and re-test at that time.</td>
<td><strong>Switching from warfarin</strong>&lt;br&gt;SPC guidance: stop warfarin, start rivaroxaban when INR is ≤3.0. <strong>EHRA guidance:</strong> initiate NOAC once INR is &lt;2.0. If INR is 2.0-2.5, start NOAC immediately or (better) next day. If INR &gt;2.5, estimate when INR is likely to drop below this threshold, and re-test at that time.</td>
<td><strong>Switching from warfarin</strong>&lt;br&gt;SPC guidance: stop warfarin, start apixaban when INR is &lt;2.0. <strong>EHRA guidance:</strong> initiate NOAC once INR is &lt;2.0. If INR is 2.0-2.5, start NOAC immediately or (better) next day. If INR &gt;2.5, estimate when INR is likely to drop below this threshold, and re-test at that time.</td>
</tr>
<tr>
<td><strong>Interactions</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><strong>Drug-food interactions</strong>&lt;br&gt;Cranberry juice and alcohol interact with warfarin. Some foods interact with warfarin (e.g. foods containing high amounts of Vitamin K).</td>
<td><strong>Drug-food interactions</strong>&lt;br&gt;There are no known food interactions.</td>
<td><strong>Drug-food interactions</strong>&lt;br&gt;There are no known food interactions.</td>
<td><strong>Drug-food interactions</strong>&lt;br&gt;There are no known food interactions.</td>
</tr>
<tr>
<td><strong>Drug-food interactions</strong>&lt;br&gt;Many interactions requiring additional INR monitoring.</td>
<td><strong>Drug-drug interactions</strong>&lt;br&gt;<strong>Contraindicated</strong> with the strong P-gp inhibitors ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedaron. Use with caution if co-administered with mild to moderate P-gp inhibitors such as amiodarone, quidine, verapamil, &amp; ticagrelor. Co-administration with P-gp inducers such as rifampicin, St John’s Wort, carbamazepine or phenytoin) should be avoided. SSRRs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups. Concomitant administration with any other anticoagulants contraindicated.</td>
<td><strong>Drug-drug interactions</strong>&lt;br&gt;Not recommended with concomitant systemic administration of strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole or HIV protease inhibitors. Strong inducers of both CYP3A4 and P-gp (such as rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s Wort) should be co-administered with caution. Concomitant administration with any other anticoagulants contraindicated.</td>
<td><strong>Drug-drug interactions</strong>&lt;br&gt;Not recommended with concomitant systemic administration of strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole or ritonavir. Strong inducers of both CYP3A4 and P-gp (such as rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s Wort) should be co-administered with caution. Concomitant administration with any other anticoagulants contraindicated.</td>
<td><strong>Drug-food interactions</strong>&lt;br&gt;Consult the SPC for full details of interactions.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Warfarin&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Dabigatran&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Rivaroxaban&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Apixaban&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>• Known hypersensitivity to warfarin or any excipients</td>
<td>• Hypersensitivity to the active substance or any excipients.</td>
<td>• Hypersensitivity to the active substance or any excipients.</td>
<td>• Hypersensitivity to the active substance or any excipients.</td>
<td>• Hypersensitivity to the active substance or any excipients.</td>
</tr>
<tr>
<td>• Haemorrhagic stroke</td>
<td>• Severe renal impairment (CrCL &lt; 30 mL/min).</td>
<td>• Active clinically significant bleeding.</td>
<td>• Active clinically significant bleeding.</td>
<td>• Active clinically significant bleeding.</td>
</tr>
<tr>
<td>• Clinically significant bleeding</td>
<td>• Active clinically significant bleeding.</td>
<td>• Any lesion or condition considered a significant risk factor for bleeding.</td>
<td>• Concomitant treatment with any other anticoagulant</td>
<td>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.</td>
</tr>
<tr>
<td>• Within 72 hours of major surgery with risk of severe bleeding</td>
<td>• Concomitant treatment with any other anticoagulant</td>
<td>• Hepatic impairment or liver disease expected to have any impact on survival.</td>
<td>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C</td>
<td>• Any lesion or condition considered a significant risk factor for bleeding.</td>
</tr>
<tr>
<td>• Within 48 hours postpartum</td>
<td>• Prosthetic heart valves</td>
<td>• Pregnancy and breast feeding.</td>
<td>• Concomitant treatment with any other anticoagulant</td>
<td>• Concomitant treatment with any other anticoagulant</td>
</tr>
<tr>
<td>• Pregnancy (first and third trimesters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Drugs where interactions may lead to a significantly increased risk of bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When should it be avoided?</td>
<td>Intolerance to warfarin including allergy, rash, side effects likely to result in discontinuation of therapy (other than bleeding complications) e.g. severe alopecia (although acenocoumarol may be a suitable alternative in these patients).</td>
<td>AVOID in patients with a history of poor medication adherence.</td>
<td>AVOID in patients with a history of poor medication adherence.</td>
<td>AVOID in patients with a history of poor medication adherence.</td>
</tr>
<tr>
<td></td>
<td>Demonstrated unmanageable warfarin control e.g. due to long term interacting drug therapy (INR persistently and significantly above or below range that does not respond to dose titration)</td>
<td>Dabigatran is <strong>not</strong> stable in compliance aids such as blister packs.</td>
<td>Rivaroxaban is <strong>not</strong> a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, drug overdose or trivial side effects related to warfarin.</td>
<td>Apixaban is <strong>not</strong> a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, drug overdose or trivial side effects related to warfarin.</td>
</tr>
<tr>
<td></td>
<td>Demonstrated impossibility of monitoring arrangements</td>
<td>Dabigatran is <strong>not</strong> a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, drug overdose or trivial side effects related to warfarin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


Acknowledgements to Jo Bateman, Cardiology Pharmacist Countess of Chester Hospital and Dave Thornton Principal Pharmacist Clinical Services University Hospital Aintree.
Adapted from original by the Regional Drug & Therapeutics Centre, October 2013.

Version number: 1.6
Last revised: March 2014