# Comparison of New Oral Anticoagulants with Warfarin - Information for Prescribers

<table>
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<tr>
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<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tr>
<td><strong>How does it work?</strong></td>
<td>Warfarin has an effect on several steps of the clotting cascade using compounds made with vitamin K by the liver.</td>
<td>Acts as a direct thrombin (factor IIa) inhibitor. It is formulated as dabigatran etexilate, a prodrug converted to dabigatran after administration.</td>
<td>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.</td>
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<td><strong>What is the evidence?</strong></td>
<td>In a meta-analysis, the RR reduction with warfarin was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%. When only ischaemic strokes were considered, adjusted-dose VKA use was associated with a 67% RRR. This reduction was similar for both primary and secondary prevention and for both disabling and non disabling strokes.</td>
<td>The RE-LY study enrolled 18,113 patients with AF, who were at increased risk of stroke. 50% of patients were naïve to oral anticoagulants. It was a prospective, open-label, blinded endpoint (PROBE) design. Dabigatran 150mg BD reduced the annual absolute risk of stroke or systemic embolism by 0.6% compared with warfarin (35% RRR) and by 0.43% (10% RRR) compared with dabigatran 110mg BD. Both haemorrhagic and ischaemic stroke occurred less often in the dabigatran 150mg BD group than with warfarin. Dabigatran was non-inferior to warfarin. Compared with warfarin, dabigatran significantly reduced the incidence of haemorrhagic, but not ischaemic stroke.</td>
<td>ROCKET-AF was a double-blind, double dummy randomized trial that enrolled 14,264 patients to either rivaroxaban 20mg od or warfarin with an INR 2-3. Patients were moderate to high risk of stroke (CHADS2 ≥2). Patients received 20mg od (15mg od if CrCl 30-49mls/min) or warfarin. Rivaroxaban was found to be non-inferior to warfarin for the prevention of stroke and systemic embolism in both the per-protocol and intention-to-treat (ITT) analysis. In the ITT analysis 2.1 events were recorded per 100 patient-years in the rivaroxaban group compared to 2.4 events with warfarin (HR 0.88, 95% CI 0.75 to 1.03, p&lt;0.001). A superiority test was pre-specified in the ITT population, but did not reach statistical significance. In the ITT population, 30% of outcome events in the rivaroxaban arm occurred after discontinuation of treatment, compared with 22% of events in the warfarin arm. This indicates a possible rebound effect, which may be related to the relatively short half life (5-13 hrs).</td>
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<td><strong>Dose and Administration</strong></td>
<td>Variable dose taken once daily dependent on INR</td>
<td>Patients under 80 years - 150mg twice daily. Patients ≥80 years - 110mg twice daily (due to the increased risk of bleeding in this population). 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 or patients weigh &lt;50kg.</td>
<td>20mg once daily. Use with caution if CrCl is 15-49 ml/min due to an increased bleeding risk.</td>
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<td><strong>Monitoring</strong></td>
<td>Needs to be adjusted to the individual needs of the patient and therefore requires regular monitoring using blood tests.</td>
<td>Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as warfarin.</td>
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Renal function should be assessed (calculate CrCl) in all patients before starting dabigatran and at least once a year in patients >75 years or those with a suspected decline in renal function. A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran.

### Safety

| Long-term safety based on 50 years use in clinical practice. | No information available on long-term safety Cannot be used if CrCl <30mls/min | No information available on long-term safety CrCl 15-49mls/min a reduced dose is recommended. Cannot be used if CrCl<15mls/min |

### Bleeding

| See respective agent for comparison | RE-LY showed; Major bleeding rates were similar for dabigatran 150mg bd and warfarin, however, major bleeding was lower with dabigatran 110mg BD than with warfarin. The incidence of GI bleeding was significantly higher with dabigatran 150mg bd (p=0.0008), but similar with dabigatran 110mg bd (p=0.52), than in patients treated with warfarin. Intracranial bleeding was uncommon but higher with warfarin. Dabigatran 150mg bd and 110mg bd reduced the absolute risk of intracranial bleeding compared with warfarin (0.32% and 0.23% respectively vs 0.76% respectively, p <0.001). A recent audit of bleeding events with dabigatran highlighted that frail, elderly patients particularly with renal impairment and low body weight are at risk of increased bleeds. | ROCKET-AF showed: No significant difference in the primary safety endpoint of major or non-major clinically relevant bleeding was seen in ROCKET-AF. GI bleeding was more common with rivaroxaban than warfarin (3.2% vs.2.2%, p=<0.001), as were a decrease in Hb of >2g/dl (4.3% vs. 3.6%, p=0.02), need for transfusion (2.6% vs. 2.1%, p=0.04), epistaxis (10.1% vs. 8.6%, p<0.05), and haematuria (4.2% vs. 3.4%, p<0.05). Intracranial haemorrhage was less common with rivaroxaban than warfarin (0.8% vs. 1.2%, p=0.02), as were critical bleeding (1.3% vs. 1.9%, p=0.007) and fatal bleeding (0.4% vs. 0.8%, p=0.003). |

### Side effects

<p>| Other side effects can include hair loss | Dyspepsia occurred at a higher rate with both doses of dabigatran, compared with warfarin. GI adverse events frequently led to drug discontinuation (7%, 6.5% and 3.9% in the dabigatran 150mg, 110mg and warfarin groups respectively). There was a non-significant increase in the number of myocardial infarctions (MI) in patients taking dabigatran compared to warfarin (0.82% for 110mg and 0.81% for 150mg vs. 0.64% p=0.12)) | There were no significant differences in the incidence of any other adverse event other than bleeding in ROCKET-AF (81% with rivaroxaban vs. 82% of warfarin patients). The most frequently reported adverse events in the rivaroxaban group were epistaxis (10%), peripheral oedema (6.1%) and dizziness (6.1%), and in the warfarin group were epistaxis (8.6%), nasopharyngitis (6.4%) and dizziness (6.3%). |</p>
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<th>Reversibility</th>
<th>Effective and well known antidote, should a severe bleed occur whilst being treated</th>
<th>No antidotes currently known. Patients with bleeding risk factors were excluded from RE-LY. Haemodialysis will clear dabigatran(^9). The serious consequences of the lack of an effective reversal agent should not be underestimated. Prolonged bleeding has increased morbidity and possibly contributed to deaths(^4).</th>
<th>No antidote currently known although prothrombin complex concentrate has been successful in showing normalisation of clotting times (APTT and thrombin times) in a small preliminary trial(^12).</th>
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| Interactions | **Drug-food interactions**  
Cranberry juice and alcohol interact with warfarin. Some foods interact with warfarin (e.g. foods containing high amounts of Vitamin K).  
**Drug-drug interactions**  
Many interactions requiring additional INR monitoring. | **Drug-food interactions**\(^7\)  
Currently there are no known food interactions.  
**Drug-drug interactions**\(^2\)  
No effect on cytochrome P450, so the potential for cytochrome P450 drug-drug interactions is low.  
There is a potential for P-gp interactions e.g. amiodarone, verapamil, quinidine, ketoconazole, clarithromycin, rifampicin, phenytoin and carbamazepine. Please see SPC for full details of interactions.  
SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups.  
Concomitant treatment with systemic and ketoconazole, cyclosporine, itraconazole and tacrolimus is C/I. Consult the SPC for full details. | **Drug-food interactions**\(^10\)  
Currently there are no known food interactions.  
**Drug-drug interactions**\(^10\)  
Not recommended with concomitant systemic treatment with azole-antimycotics e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp.  
Strong CYP3A4 inducers should be co-administered with caution (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) as they may lead to reduced rivaroxaban concentrations.  
For full details of interactions consult the SPC. |
| Contraindications | • Haemorrhagic stroke  
• Clinically significant bleeding  
• Within 72 hours of major surgery with risk of severe bleeding (for information on other surgery)  
• Within 48 hours postpartum  
• Pregnancy (first and third trimesters) | • Severe renal impairment (CrCL < 30 ml/min)  
• Active clinically significant bleeding  
• Organic lesion at risk of bleeding  
• Spontaneous or pharmacological impairment of haemostasis  
• Hepatic impairment or liver disease expected to have any impact on survival  
• Pregnancy and breastfeeding\(^2\) | • Hypersensitivity to the active substance or to any of the excipients.  
• Clinically significant active bleeding.  
• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C  
• Pregnancy and breast feeding  
• CrCl <15mls/min is contraindicated\(^10\) |

A meta-analysis\(^8\) combining 7 studies showed dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group. The control group varied and included enoxoparin, warfarin and placebo\(^8\). The rate of MI was numerically, but not statistically significantly lower in the rivaroxaban arm compared with the warfarin group\(^11\).
### When should it be avoided?

| 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). | AVOID dabigatran in patients with a history of poor medication adherence. Dabigatran is not stable in compliance aids such as blister packs. AVOID in patients with severe renal impairment and patients with liver disease or severe hepatic impairment. Dabigatran is not 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. Please see the CMCSN statement on dabigatran. |
| 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) | AVOID rivaroxaban in patients with a history of poor medication adherence. AVOID in patients with CrCl <15mls/min and caution if CrCl 15-29mls/min. AVOID in patients with liver disease or severe hepatic impairment. Rivaroxaban is not 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. Please see the CMCSN statement on rivaroxaban. |

### This information is a summary to guide prescribers – please consult individual SPC’s for further information at [www.medicines.org.uk](http://www.medicines.org.uk)

### References


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