# Comparison of Anticoagulants (DOACs and warfarin)

For guidance – for full information refer to individual SPCs available at [www.medicines.org.uk](http://www.medicines.org.uk)

The tables in the rest of this document highlight the differences between the different DOACs and warfarin.

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# Comparison of Anticoagulants (DOACs and warfarin)

| Licensed indication and NICE recommendations  |
| --- |
|  | **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,**6 |
| Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension1,2,3,4 | √NICE TA 2497 | √NICE TA 2568 | √NICE TA 2759 | √NICE TA 35510 | √ |
| Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults1,2,3,4 | √NICE TA 32711 | √NICE TA 26112 and 28713 | √NICE TA 34114 | √NICE TA 35415 | √ |
| Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery1,2,3  | √NICE TA 15716 | √ 10mg onlyNICE TA 17017 | √NICE TA 24518 | x | √ |
| Co-administered with acetylsalicylic acid\* (ASA) alone or with ASA plus clopidogrel or ticlopidine, indicated for prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers2\*acetylsalicylic acid (ASA) = Aspirin | x | √ 2.5mg onlyNICE TA 35519 | x | x | x |
| Co-administered with acetylsalicylic acid (ASA) is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events2\*acetylsalicylic acid (ASA) = Aspirin | x | √ 2.5mg onlyNICE TA 60720 | x | x | x |
| Transient cerebral ischaemic attacks | x | x | x | x | √ |

| Mode of action |
| --- |
| **Dabigatran (Pradaxa®)1,5** | **Rivaroxaban (Xarelto®▼)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Direct thrombin inhibitor | Direct inhibitor of factor Xa | Direct inhibitor of factor Xa | Direct inhibitor of factor Xa | Inhibits the synthesis of vitamin K dependent clotting factors, which include factors II, VII, IX and X, and the anticoagulant proteins C and S |

| Preparation (oral tablets or capsules) |
| --- |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®▼)2,6** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5** |
| 75mg, 110mg and 150mg capsules (gelatin free) | 2.5mg, 10mg, 15mg and 20mg tablets | 2.5mg and 5mg tablets  | 15mg, 30mg and 60mg tablets | 0.5mg, 1mg, 3mg, 5mg tablets |

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| Difficulty swallowing medication  |
| **Dabigatran (Pradaxa®)1** | Do not open the capsule as this may increase the risk of bleeding due to increased bioavailability of dabigatran etexilate. |
| **Rivaroxaban (Xarelto®▼)2** | Tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. The crushed tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in 50ml of water via a gastric tube after which it should be flushed with water.After the administration of crushed 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding. |
| **Apixaban (Eliquis®)3** | Tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered.Alternatively, tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube.Crushed tablets are stable in water, D5W, apple juice, and apple puree for up to four hours. |
| **Edoxaban (Lixiana®)4** | Tablets may be crushed and mixed with water or apple puree and immediately administered orally. Tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water.Crushed tablets are stable in water and apple puree for up to 4 hours. |
| **Warfarin5** | Tablets may be crushed and/or dispersed in water or crushed and given with soft food.Warfarin 1mg/1ml oral suspension is available as a licensed preparation. It does not require fridge storage and has an expiry of 28 days once opened.21 |

# Calculating DOAC dosages

# Renal function

All DOACs are dependent on renal function for elimination. Dosages for all DOACs should be based on the estimated creatinine clearance (CrCl).1-4

Renal function should be assessed prior to initiation and at least once a year, or more frequently as needed in certain situations. For example every one to three months when it is suspected that the renal function could decline or deteriorate, e.g. due to hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products.1,22 Note: In practice eGFR and CrCl are not interchangeable; however for average build and height, eGFR could provide some guidance.6 The Summary of Product Characteristics (SPCs) for Pradaxa® (dabigatran) and Lixiana® (edoxaban), specify that the method used to estimate renal function (creatinine clearance - CrCl in mL/min) is the Cockcroft-Gault method.1,4 The Cockcroft-Gault equation is given below6:

**CrCl = [140 – age (years)] x weight\* (kg) x (1.23 for males or x 1.04 for females)**

**Serum creatinine (micromole/l**)

\* **Weight**: The MD+Calc site states:

Based on several papers and expert opinions, we provide adjustments to the Cockcroft-Gault equation based on body weight and BMI, as it appears to become less accurate in weight extremes (underweight and particularly overweight/obesity). Adjustments and estimates are made as follows:23:

|  |  |  |
| --- | --- | --- |
| Underweight | BMI <18.5 | Use actual body weight |
| Normal weight | BMI 18.5-24.9 | Use ideal body weight |
| Overweight / obese | BMI ≥25 | Use adjusted body weight |

However the MDCalc online calculator acknowledges that controversy exists over which form of weight to use and therefore, where height is also included, offers a range of creatinine clearance values to support making a clinical decision for individual patients, based on ideal, actual and adjusted weights. Where a difference exists in the CrCl values calculated that would mean two different doses could be used, a decision should be made on an individual patient basis with advice from the consultant if appropriate.

Ideal body weight (IBW) and adjusted body weight (ABW)are calculated as follows:

IBW, kg (male) = 50 + [ 2.3 × (height, inches – 60)

IBW, kg (female) = 45.5 + [ 2.3 × (height, inches – 60)

ABW, kg = IBW, kg + 0.4 × (actual body weight, kg – IBW, kg)

It is important to note that the CrCl calculations in the clinical trials for all DOACs used actual body weight for all patients rather than ideal or adjusted body weight. Dosing of the DOACs in the SPCs are therefore based on CrCl calculations using actual body weight. Using ideal body weight in patients may therefore result in [under dosing](https://www.amjmed.com/article/S0002-9343%2817%2930481-3/fulltext), particularly in those that are overweight or obese.

Many local guidelines have been developed which use actual body weight for patients with a BMI ≤30kg/m2 and using adjusted body weight for those above this threshold. There is no national guidance available on this issue, therefore, local guidance should be followed on which weight to use in the calculations.

An on-line calculator can be used to calculate the creatinine clearance using the Cockcroft-Gault equation. This is found at: MD+CALC <https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation>23 The Cockcroft and Gault formula is also available in the BNF.6

On-line calculators are also available for ideal body weight and adjusted body weight calculations. Refer to MD+CALC <https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight>

GP practice clinical systems can also be used to calculate creatinine clearance but prescribers must be aware of defaults in the calculation i.e. ideal or actual body weight. If calculated externally, creatinine clearance can be coded into GP clinical systems using the [SNOMED code](https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct) 968191000000100.

NG196 does not suggest a preferred DOAC in people with renal impairment, but does advise that BNF guidance on dosages in people with renal impairment are followed.24 NG158 states that people with confirmed proximal DVT or PE and renal impairment (CrCl 15-50ml/min) should be offered one of: apixaban, rivaroxaban, LMWH for at least five days then edoxaban or dabigatran, LMWH or UFH with warfarin for at least five days then warfarin alone.25

The NICE guideline for chronic kidney disease in adults: assessment and management [NG203] recommends that healthcare professionals should consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50ml/min/1.73m2 and NVAF who have one or more specified risk factors for stroke.26

The SPC for edoxaban states that, when used for preventing stroke and systemic embolism in people with NVAF, a trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared with well-managed warfarin. Therefore, edoxaban should be used in people with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.4

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| **Dosages in renal impairment**  |
|  | **Dabigatran (Pradaxa®)1,27** | **Rivaroxaban (Xarelto®▼)2,27** | **Apixaban (Eliquis®)3,27** | **Edoxaban (Lixiana®)4,27** | **Warfarin5,6** |
| CrCl >80ml/min | No dosage adjustment | No dosage adjustment | No dosage adjustment | No dosage adjustment | No dosage adjustment |
| CrCl50-80ml/min | No dosage adjustment | No dosage adjustment | 2.5mg bd for some patients\* | No dosage adjustment | Use with caution |
| CrCl30-49ml/min | Primary prevention of VTE in orthopaedic surgery - single capsule of 75mg followed by 150mg daily AF, DVT & PE - no dosage adjustment unless bleeding risk, then reduce to 110mg twice daily | 15mg daily | 2.5mg bd for some patients\* | 30mg daily | Use with caution |
| CrCl15-29ml/min | Contraindicated | Caution - 15mg daily | 2.5mg bd for prevention of stroke and systemic embolism in patients with NVAFUse with caution for other indications | 30mg daily | Monitor INR more frequently |
| CrCl <15ml/min | Contraindicated | Use not recommended | Use not recommended | Use not recommended | Monitor INR more frequently |
| Notes |  | When dose is 10mg daily, no dosage adjustment necessary | \*For prevention of stroke and systemic embolism in patients with NVAF in patients with serum creatinine ≥1.5mg/dL (133micromole/L), age ≥80 years or body weight ≤60kg |  |  |

| Dose in AFDuration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Do not stop anticoagulation solely because AF is no longer detectable. Base decisions to stop anticoagulation on a reassessment of stroke and bleeding risk using CHA2DS2VASc and ORBIT and a discussion of the patients preferences.24**Warfarin treatment is usually long term.** |
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| **Dabigatran (Pradaxa®)1** | < 80 years: 150mg twice daily≥80 years or also on verapamil: 110mg twice daily after individual assessment of thromboembolic and bleeding risk 150mg twice daily or 110mg twice daily should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding for following:* Age 75-80 years
* CrCl 30-50ml/min
* Patients with gastritis, esophagitis or gastroesophageal reflux

Other patients at increased risk of bleeding |
| **Rivaroxaban (Xarelto®▼)2** | 20mg dailyIn patients with CrCl 30–49ml/min or CrCl 15–29ml/min, reduce dose to 15mg daily  |
| **Apixaban (Eliquis®)3** | 5mg twice daily 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 micromole/L) |
| **Edoxaban (Lixiana®)4** | 60mg dailyReduce dose to 30mg with one or more of following risk factors:Moderate to severe renal impairment (CrCl 15-50ml/min)Body weight ≤60kgConcomitant use of P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole) |
| **Warfarin5,6** Dose is tailored to the individual, dependent on the prothrombin time (PT) | Target INR 2.5 Typical induction dose of warfarin is 10mg daily for 2 daysBaseline PT should be taken at outsetDaily maintenance dose of warfarin is usually 3mg to 9mg dependent on PT or other anticoagulation tests5 |

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| Dose in treatment and prevention of DVT and PE |
| Short duration of therapy (at least three months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.4 Assess anticoagulation after three months after a proximal DVT or PE (three to six months with active cancer). Consider stopping after a provoked DVT if provoking factor is no longer present.25Consider continuing anticoagulation beyond three months (six months for people with active cancer) after an unprovoked DVT or PE. Discuss the risks and benefits of long-term anticoagulation with the person and take their preferences into account.25 |
| **Warfarin duration** Six weeks in people with distal DVT (calf vein thrombosis).Three months in people with proximal DVT or PE where there are known temporary risk factors ***and***there is considered to be a low risk of recurrence.Six months in people with proximal DVT due to an unknown cause (idiopathic).Long term if there have been recurrent DVTs or PEs.Warfarin can be stopped abruptly without harm when the duration of treatment is completed.22 |
| **Dabigatran (Pradaxa®)1** | 150mg twice daily following treatment with a parenteral anticoagulant for at least five daysIf ≥80 years or also on verapamil: 110mg twice daily after individual assessment of thromboembolic and bleeding risk 150mg twice daily or 110mg twice daily should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding for following:* Age 75-80 years
* CrCl 30-50ml/min
* Patients with gastritis, esophagitis or gastroesophageal reflux
* Other patients at increased risk of bleeding
 |
| **Rivaroxaban (Xarelto®▼)2** | 15mg twice daily for days 1 to 21, then 20mg daily |
| **Apixaban (Eliquis®)3** | Treatment: 10mg twice daily for the first seven days, followed by 5mg twice dailyPrevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE: 2.5mg twice daily  |
| **Edoxaban (Lixiana®)4** | 60mg daily following parenteral anticoagulant for at least five daysReduce dose to 30mg with one or more of following risk factors:* Moderate to severe renal impairment
* Body weight ≤60kg
* Concomitant use of P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole)
 |
| **Warfarin5,6** Dose is tailored to the individual, dependent on the prothrombin time (PT) | Target INR 2.5 for treatment of deep-vein thrombosis or pulmonary embolismTarget INR 3.5 for recurrent deep-vein thrombosis or pulmonary embolism in patients currently receiving anticoagulation and with an INR above 2 |
| VTE prevention post-surgery |
| For prevention of VTE after major elective orthopaedic surgery (i.e. knee or hip replacement) ensure DOACs are stopped in accordance with instructions in the discharge letter or when the licensed duration of treatment period is reached.1-3,6 |
| **Dabigatran (Pradaxa®)1** | Single dose of 110mg 1-4 hrs after surgery, then 220mg once daily for:10 days post knee surgery4 to 5 weeks post hip surgeryReduce dose for patients with: * CrCl 30-50ml/min
* Patients who receive concomitant verapamil, amiodarone, quinidine
* Patients aged 75 years and above

Give a single dose of 75mg 1-4 hrs after surgery, then 150mg daily for:* 10 days post knee surgery
* 4 to 5 weeks post hip surgery

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily |
| **Rivaroxaban (Xarelto®▼)2** | 10mg once daily for:* 2 weeks post knee surgery
* 5 weeks post hip surgery
 |
| **Apixaban (Eliquis®)3** | 2.5mg twice daily for:* 10 to 14 days post knee surgery
* 32 to 38 days post hip surgery
 |
| **Edoxaban (Lixiana®)4** | Not licensed |
| **Warfarin5,6** | Not licensed |

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| Acute coronary syndrome  |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2,6** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Not licensed | 2.5mg twice daily with aspirin alone or aspirin + clopidogrel or ticlopidineReview regularlyExtension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited | Not licensed | Not licensed | Not licensed |

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| Dosage in extremes of body weight |
|  | **Dabigatran (Pradaxa)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Low body weight | No dosage adjustment, but close clinical surveillance if <50Kg | No dosage adjustment | NVAF - 2.5mg twice daily if ≤60Kg; VTE – no dosage adjustment | ≤60Kg - NVAF and VTE 30mg daily | Loss of weight may require a dose reduction |
| >120Kg | No dosage adjustment | No dosage adjustment | No dosage adjustment | No dosage adjustment | Weight gain may require dosage increase |

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| Method of administration |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| With or without food | With food | With or without food | With or without food | With or without food |

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| [Reversibility](#Reversal)1-6 (Also see reversal of anticoagulation below)  |
| **Dabigatran (Pradaxa®)1** | Idarucizumab (Praxbind®) Priced at £2,400 per dose (2 x 50g vials)6,28 |
| **Rivaroxaban (Xarelto®▼)2** | Andexanet alfa (Ondexxya®) Priced at £11,100 for 4 vials of 200mg powder for solution for infusionLow dose – 5 vials = £13,875 High dose – 9 vials = £24,9756,29Activated charcoal may be considered |
| **Apixaban (Eliquis®)3** | Andexanet alfa (Ondexxya®)Priced at £11,100 for 4 vials of 200mg powder for solution for infusion Low dose – 5 vials = £13,875 High dose – 9 vials = £24,9756,29Prothrombin complex concentrates (PCC) or recombinant factor VIIa may be considered for life threatening situations |
| **Edoxaban (Lixiana®)4** | No antidote Early administration of activated charcoal may be considered in case of edoxaban overdose to reduce absorptionFor life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion. Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban. |
| **Warfarin5** | Major bleeding - stop warfarin give phytomenadione (vitamin K1) by slow intravenous injection; give dried prothrombin complex (factors II, VII, IX, and X); if dried prothrombin complex unavailable, fresh frozen plasma can be given but is less effective; recombinant factor VIIa is not recommended for emergency anticoagulation reversal6INR >8.0, minor bleeding - stop warfarin sodium; give phytomenadione(vitamin K1) by slow intravenous injection; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin sodium when INR <5.06INR >8.0, no bleeding - stop warfarin sodium; give phytomenadione (vitamin K1) by mouth using the intravenous preparation orally [unlicensed use]; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR <5.06INR 5.0–8.0, minor bleeding – stop warfarin sodium; give phytomenadione (vitamin K1) by slow intravenous injection; restart warfarin sodium when INR <5.06INR 5.0–8.0, no bleeding - withhold 1 or 2 doses of warfarin sodium and reduce subsequent maintenance dose6Unexpected bleeding at therapeutic levels - always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology6 |

##

## Reversal of anticoagulation

**Warfarin**

The effects of warfarin can be reversed with phytomenadione in combination with dried prothrombin complex or fresh frozen plasma.6

**DOACs**

Specific reversal agents are now available for dabigatran (idarucizumab - Praxbind®), apixaban and rivaroxaban (andexanet alfa - Ondexxya▼).28,29 These are discussed further:

**Dabigatran**

Idarucizumab is licensed to reverse the anticoagulant effects of dabigatran.28 In the interim analysis of the RE-VERSE AD study, NICE states that people may still need other supportive measures, for example blood products, to manage their bleeding and these should be considered as medically appropriate.30

The SPC provides the results of RE-VERSE AD study (n= 503 patients: 301 patients with serious bleeding (Group A) and 202 patients requiring an urgent procedure/surgery (Group B)). Restoration of haemostasis was achieved in 80.3% of evaluable patients who had serious bleeding and normal haemostasis was observed in 93.4% of patients who required an urgent procedure. Of the total 503 patients, 101 patients died; each of these deaths could be attributed to either a complication of the index event, or co-morbidities. Thrombotic events were reported in 34 patients (23 out of the 34 patients were not on antithrombotic therapy at the time of the event) and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established.28

**Rivaroxaban and apixaban**

Andexanet alfa is licensed to reverse the anticoagulant effects of rivaroxabanandapixaban.29 Because of the limitations of the clinical evidence, the cost-effectiveness estimates for andexanet alfa are uncertain. Therefore, andexanet alfa for reversing anticoagulation is recommended for routine use only in gastrointestinal bleeding. It is recommended only in research in intracranial haemorrhage (ICH).31

**Edoxaban**

A specific antidote antagonising the pharmacodynamic effect of edoxaban is not available**.** Early administration of activated charcoal may be considered in case of edoxaban overdose to reduce absorption. This recommendation is based on standard treatment of medicinal product overdose and data available with similar compounds, as the use of activated charcoal to reduce absorption of edoxaban has not been specifically studied in the edoxaban clinical programme. For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion. Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban.4

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| Conversion from warfarin to DOAC |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Discontinue warfarin and start dabigatran when INR <2 | Discontinue warfarin and start rivaroxaban when: INR ≤3 for prevention of stroke and systemic embolismINR ≤2.5 for DVT, PE and prevention of recurrence | Discontinue warfarin and start apixaban when INR <2 | Discontinue warfarin and start edoxaban when INR is ≤2.5 | N/A |

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| Conversion from DOAC to warfarin |
| **Dabigatran (Pradaxa®)1** | Adjust the starting time of the warfarin based on CrCl as follows:CrCl ≥ 50mL/min, start warfarin 3 days before discontinuing dabigatran etexilateCrCl ≥30 - <50 mL/min, start warfarin 2 days before discontinuing dabigatran etexilateAs dabigatran can increase INR, the INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution |
| **Rivaroxaban (Xarelto®▼)2** | Warfarin should be given concurrently until the INR is ≥ 2.0 For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing, as guided by INR testing While patients are on both rivaroxaban and warfarin the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose |
| **Apixaban (Eliquis®)3** | Continue administration of apixaban for at least 2 days after beginning warfarin therapy After 2 days of co-administration of apixaban with warfarin therapy, obtain an INR prior to the next scheduled dose of apixabanContinue co-administration of apixaban and warfarin therapy until the INR is ≥2.0 |
| **Edoxaban (Lixiana®)4** | 60mg dose: Administer 30mg + warfarin30mg dose: Administer 15mg + warfarinDo not take loading dose of warfarin in order to promptly achieve INR 2-3 Take account of maintenance dose of warfarin and if patient was previously taking warfarin or use validated INR driven warfarin treatment algorithmWhen INR ≥2, discontinue edoxaban. Most patients should be able to achieve INR ≥2 within 14 days of edoxaban + warfarin. After 14 days discontinue edoxaban and titrate warfarin to achieve INR 2-3 |

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| Conversion from DOAC to edoxaban |
| **Dabigatran (Pradaxa®)1** | Stop dabigatran and start edoxaban when the next dose of dabigatran would have been due4,21If higher therapeutic plasma concentrations are expected, e.g. impaired renal function, a longer interval between dabigatran stopping and edoxaban starting is recommended21  |
| **Rivaroxaban (Xarelto®▼)2** | Stop rivaroxaban and start edoxaban when the next dose of rivaroxaban would have been due4,21If higher therapeutic plasma concentrations are expected, e.g. impaired renal function, a longer interval between rivaroxaban stopping and edoxaban starting is recommended21  |
| **Apixaban (Eliquis®)3** | Stop apixaban and start edoxaban when the next dose of apixaban would have been due4,21 If higher therapeutic plasma concentrations are expected, e.g. impaired renal function, a longer interval between apixaban stopping and edoxaban starting is recommended21  |

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| Conversion from parenteral anticoagulant to oral anticoagulant |
| **Dabigatran (Pradaxa®)1** | Discontinue the parenteral anticoagulant Start dabigatran 0-2 hours prior to the time that the next dose of the parenteral anticoagulant would be due, **or** Start dabigatran at the time of discontinuation in case of continuous treatment (e.g. intravenous unfractionated heparin) |
| **Rivaroxaban (Xarelto®▼)2** | Discontinue the parenteral anticoagulant Start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparin (LMWH)) would be due, **or** Start rivaroxaban at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin) |
| **Apixaban (Eliquis®)3** | Switching treatment from parenteral anticoagulants to apixaban (and vice versa) can be done at the next scheduled dose |
| **Edoxaban (Lixiana®)4** | Discontinue subcutaneous anticoagulant (e.g. LMWH)Start edoxaban at the time of the next scheduled subcutaneous anticoagulant doseDiscontinue intravenous unfractionated heparin infusionStart edoxaban 4 hours later |
| **Warfarin5,6** | Start warfarin and stop LMWH/unfractionated heparin once INR is in therapeutic range for 2 consecutive days  |

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| Missed dose (Also refer to half-life below) |
| **Dabigatran (Pradaxa®)1** | May still be taken up to six hours prior to the next scheduled doseFrom 6 hours prior to the next scheduled dose onwards, the missed dose should be omittedNo double dose should be taken to make up for missed individual doses |
| **Rivaroxaban (Xarelto®▼)2** | Take missed dose immediately and then continue the following day with once daily intake as recommendedDo not double the dose within the same day to make up for a missed doseHowever, if taking 15mg twice daily for DVT/PE treatment (days 1-21) and a dose is missed, take 15mg immediately to ensure intake of 30mg daily, this may mean 2 x 15mg tablets are taken at once, then continue with 15mg twice daily the following dayIf a dose is missed during the once daily treatment phase (day 22 onwards), take dose immediately and continue the next day with once daily intake Do not double the dose within the same day to make up for a missed dose |
| **Apixaban (Eliquis®)3** | Take missed dose immediately and then continue with twice daily intake as before |
| **Edoxaban (Lixiana®)4** | Take missed dose immediately then continue with once daily dose Do not double the prescribed dose on the same day |
| **Warfarin5,6** | If a missed dose is remembered before midnight, the dose can still be takenIf the dose is forgotten for a longer time, do not take the dose to catch up, but take the next dose when it is dueNever take a double dose of warfarin to make up for a missed dose32 |

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| Half-life (t½) |
| **Dabigatran (Pradaxa®)1** | Terminal half-life in healthy elderly subjects – 11 hoursTerminal half-life after multiple doses - 12-14 hours |
| **In renal impairment** | **Half-life (hours, range)** | 13.4(11.0 - 21.6) | 15.3 (11.7 - 34.1) | 18.4(13.3 - 23) | 27.2(21.6 - 35) |
| **CrCl (ml/min)** | ≥80 | ≥50 - <80 | ≥30 - <50 | <30 |
| **Rivaroxaban (Xarelto®▼)2** | Terminal half-life in young individuals - 5-9 hoursTerminal half-life in the elderly - 11-13 hours |
| **Apixaban (Eliquis®)3** | Approximately 12 hours |
| **Edoxaban (Lixiana®)4** | 10 to 14 hours |
| **Warfarin5,6** | Single dose - approximately one week * Effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours
* Studies with radiolabelled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine, very little warfarin is excreted unchanged in urine, and urinary excretion is in the form of metabolites
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| Bioavailability |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®▼)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| 6.5% | 2.5mg and 10mg:* 80-100% in fasting and fed conditions

15mg/20mg:* 66% without food
* 100% with food
 | 50% | 62% | 100% |

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| Protein binding |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®▼)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5** |
| 34-35% | 92-95% | 87% | 55% | 99% |

| Hepatic impairment |
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| (Hepatic disease-coagulopathy, bleeding risk including cirrhotic patients with Child-Pugh Score B and C) |
|  | **Hepatic impairment** | **Patients with elevated liver enzymes >2 ULN (Upper limit of normal)** |
| **Dabigatran (Pradaxa®)1** | Contraindicated in hepatic impairment or liver disease where expected to have impact on survival | Not recommended |
| **Rivaroxaban (Xarelto®▼)2** | Contraindicated in hepatic disease  | Not stated |
| **Apixaban (Eliquis®)3** | Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding riskSevere – not recommendedMild to moderate - caution | Caution - also applies if total bilirubin ≥1.5 x ULNLFTs needed prior to initiating  |
| **Edoxaban (Lixiana®)4** | Contraindicated in hepatic diseaseSevere – not recommendedMild to moderate - caution | Caution - also applies if total bilirubin ≥1.5 x ULNLFTs needed prior to initiating |
| **Warfarin5,6** | Severe impairment - avoidMild to moderate - caution  | Not stated |

| Drug interactions |
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| Use individual medicines [SPC](https://www.medicines.org.uk/emc/) and the drug interactions table in the BNF for a complete list <https://bnf.nice.org.uk/interaction/>  |

| Contraindications |
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| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5** |
| Hypersensitivity to the active substance or to any of the excipients |
| Clinically significant active bleeding |
| Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities | Within 72 hours of major surgery with risk of severe bleeding, Haemorrhagic stroke |
| Concomitant treatment with any other anticoagulants e.g. UFH, LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter |  |
| Liver disease associated with coagulopathy and clinically relevant bleeding risk |  |
| Hepatic impairment or liver disease expected to have any impact on survival | Hepatic disease associated with coagulopathy and clinically relevant bleeding risk |  |
|  | Pregnancy and breast-feeding |  | Pregnancy and breast-feeding | Within 48 hours postpartum, Pregnancy (first and third trimesters) |
|  |  |  | Uncontrolled severe hypertension |  |
| Severe renal impairment (CrCl <30 mL/min) in adult patients |  |  |  |  |
| eGFR <50 mL/min/1.73m2 in paediatric patients |  |  |  |  |
| Prosthetic heart valves requiring anticoagulant treatment |  |  |  |  |
| Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir |  |  |  | Drugs where interactions may lead to a significantly increased risk of bleeding |

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| Prosthetic heart valves |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5** |
| Contra-indicated | Not studied – not recommended | Not studied – not recommended | Not studied – not recommended | Target INR 2.5 -Licensed for prophylaxis after insertion of prosthetic heart valves |

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| Antiphospholipid syndrome  |
| The TRAPS trial compared rivaroxaban with warfarin in patients with antiphospholipid syndrome and a history of thrombosis. The study was terminated prematurely as there was an increased risk of recurrent thromboembolic events associated with rivaroxaban. Available data show that other DOACs may be associated with a similarly increased risk. Consequently, DOACs are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all three antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies).33 |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Not recommended | Not recommended | Not recommended | Not recommended | Target INR 2.5Suitable for treatment of deep-vein thrombosis or pulmonary embolism (including those associated with antiphospholipid syndrome) |

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| Compliance aids |
| **Dabigatran (Pradaxa®)1** | **Rivaroxaban (Xarelto®**▼**)2** | **Apixaban (Eliquis®)3** | **Edoxaban (Lixiana®)4** | **Warfarin5,6** |
| Store in the original package in order to protect from moisture | No special precautions for storage | No special precautions for storage | No special precautions for storage | Not recommended for compliance aid as dose may vary depending on test results |

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| Cost per 28 days at dose stated34  |
| (This is the NHS List price and not the nationally commissioned discounted or local rebate price. These can be inserted locally below) |
| **Dabigatran (Pradaxa®)1****150mg twice daily** | **Rivaroxaban (Xarelto®**▼**)2 20mg once daily** | **Apixaban (Eliquis®)3****5mg twice daily** | **Edoxaban (Lixiana®)4****60mg once daily** | **Warfarin5,6****3mg daily** |
| £47.60 | £50.40 | £53.20 | £49.00 | £0.73 + monitoring |
| £47.60 | £Nationally commissioned cost | £Nationally commissioned cost | £Nationally commissioned cost | £0.73 + monitoring |

## References

1. Summary of Product Characteristics - Pradaxa 150mg hard capsules, Boehringer Ingelheim Limited. Date of revision of the text 01/01/2021. <https://www.medicines.org.uk/emc/product/4703>
2. Summary of Product Characteristics – Xarelto 15mg film-coated tablets, Bayer plc. Date of revision of the text September 2021. <https://www.medicines.org.uk/emc/product/2794>
3. Summary of Product Characteristics – Eliquis 2.5mg film-coated tablets, Bristol-Myers Squibb-Pfizer. Date of revision of the text 16/02/22. <https://www.medicines.org.uk/emc/product/4756>
4. Summary of Product Characteristics – Lixiana 30mg film-coated tablets, Daiichi Sankyo UK Limited. Date of revision of the text 6/11/20. <https://www.medicines.org.uk/emc/product/6906>
5. Summary of Product Characteristics – Warfarin 0.5mg tablets. Ranbaxy (UK) Limited a Sun Pharmaceutical Company. Date of revision of the text 07/12/21. <https://www.medicines.org.uk/emc/product/3064>
6. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. <https://www.medicinescomplete.com/> Accessed February 2022.
7. NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. Technology Appraisal guidance [TA249]. Published March 2012, last updated July 2021. [www.nice.org.uk/guidance/ta249](http://www.nice.org.uk/guidance/ta249)
8. NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. Technology appraisal guidance [TA256]. Published May 2012, last updated July 2021. [www.nice.org.uk/guidance/ta256](http://www.nice.org.uk/guidance/ta256)
9. NICE. Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Technology appraisal guidance [TA275]. Published Feb 2013, last updated July 2021. [www.nice.org.uk/guidance/ta275](http://www.nice.org.uk/guidance/ta275)
10. NICE. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Technology appraisal guidance [TA355]. Published Sep 2015, last updated July 2021. [www.nice.org.uk/guidance/ta355](http://www.nice.org.uk/guidance/ta355)
11. NICE. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Technology appraisal guidance [TA327]. Published December 2014. [www.nice.org.uk/guidance/ta327](http://www.nice.org.uk/guidance/ta327)
12. NICE. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. Technology appraisal guidance [TA261]. Published July 2012. [www.nice.org.uk/guidance/ta261](http://www.nice.org.uk/guidance/ta261)
13. NICE. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. Technology appraisal guidance [TA287]. Published June 2013. [www.nice.org.uk/guidance/ta287](http://www.nice.org.uk/guidance/ta287)
14. NICE. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Technology appraisal guidance [TA341]. Published June 2015. <https://www.nice.org.uk/guidance/ta341>
15. NICE. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism. Technology appraisal guidance [TA354]. Published August 2015. [www.nice.org.uk/guidance/ta354](http://www.nice.org.uk/guidance/ta354)
16. NICE. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. Technology appraisal guidance [TA157]. Published September 2008. [www.nice.org.uk/guidance/ta157](http://www.nice.org.uk/guidance/ta157)
17. NICE. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. Technology appraisal guidance [TA170]. Published April 2009. [www.nice.org.uk/guidance/ta170](http://www.nice.org.uk/guidance/ta170)
18. NICE. Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. Technology appraisal guidance [TA245]. Published January 2012. [www.nice.org.uk/guidance/ta245](http://www.nice.org.uk/guidance/ta245)
19. NICE. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. Technology appraisal guidance [TA335]. Published March 2015. <https://www.nice.org.uk/guidance/ta335>
20. NICE. Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease. Technology appraisal guidance [TA607]. Published October 2019. <https://www.nice.org.uk/guidance/ta607>
21. Summary of Product Characteristics – Warfarin Sodium 1mg/ml oral solution. Rosemont Pharmaceuticals Limited. Date of revision of the text 25/01/2022. <https://www.medicines.org.uk/emc/product/5766/smpc>
22. NICE Clinical Knowledge Summary. Anticoagulation – oral. Last revised May 2022. <https://cks.nice.org.uk/topics/anticoagulation-oral/>
23. MD+CALC. Creatinine clearance (Cockcroft-Gault equation). <https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation>
24. NICE. Atrial fibrillation: diagnosis and management. NICE guideline [NG196]. Published April 2021, last updated June 2021. <https://www.nice.org.uk/guidance/ng196>
25. NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE guideline [NG158]. Published March 2020. <https://www.nice.org.uk/guidance/ng158>
26. NICE. Chronic kidney disease: assessment and management. NICE guideline [NG203]. Published August 2021, last updated November 2021. <https://www.nice.org.uk/guidance/ng203>
27. DOAC dose adjustment in renal impairment. Drug and Therapeutics Bulletin 2020; 58(9): 131. <https://dtb.bmj.com/content/early/2020/06/15/dtb.2020.000038>
28. Summary of Product Characteristics - Praxbind 2.5g/50mL solution for injection/infusion. Boehringer Ingelheim Limited. Date of revision of the text September 2020. <https://www.medicines.org.uk/emc/product/5073>
29. Summary of Product Characteristics - Ondexxya 200mg powder for solution for infusion. AstraZeneca UK Limited. Date of revision of the text 1 June 2022. <https://www.medicines.org.uk/emc/product/10933/>
30. NICE. Reversal of the anticoagulant effect of dabigatran: idarucizumab. Evidence Summary [ESNM73]. Published May 2016. <https://www.nice.org.uk/advice/esnm73/chapter/Key-points-from-the-evidence>
31. NICE. Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Technology appraisal guidance [TA697]. Published May 2021. <https://www.nice.org.uk/guidance/ta697>
32. Patient Leaflet - Warfarin 0.5mg tablets. Ranbaxy (UK) Limited a Sun Pharmaceutical Company. Last updated on emc 09 Dec 2021. <https://www.medicines.org.uk/emc/product/3064/pil>
33. Drug Safety Update. Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome. Published June 2019. <https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-increased-risk-of-recurrent-thrombotic-events-in-patients-with-antiphospholipid-syndrome>
34. NHS Business Services Authority. Drug Tariff June 2022. <https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff>