Comparison of novel oral anticoagulants (NOACs)

For guidance – for full information refer to individual SPCs available at www.medicines.org.uk

Licensed indications for NOACs

- 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; hypertension.[1,2,3,4]
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.[1,2,3,4]
- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery – only dabigatran, rivaroxaban and apixaban (but not edoxaban) are licensed and approved by NICE.[1,2,3]
- Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers – Rivaroxaban only.[2]

The tables in the rest of this document highlight the differences between the different NOACs.

Contents

Action			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Inhibits clot formation by inhibiting thrombin activity	Direct inhibitor of Factor Xa	Direct inhibitor of Factor Xa	Direct inhibitor of Factor Xa

Preparation (oral tablets or capsules)			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
75mg, 110mg and 150mg	2.5mg, 10mg, 15mg and 20mg	2.5mg and 5mg	15mg, 30mg and 60mg

Dose in AF

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Dabigatran (Pradaxa®)[1]	Rivaroxaban (Xarelto®)[2]	Apixaban (Eliquis®)[3]	Edoxaban (Lixiana®)[4]

• < 80yrs: 150mg twice daily
• ≥80yrs 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 75-80yrs
  ○ CrCl 30-50ml/min
  ○ Patients with gastritis, esophagitis or gastroesophageal reflux
  ○ Other patients at increased risk of bleeding
	• 20mg daily
	• In patients with CrCl 30 – 49 ml/min or CrCl 15 – 29 ml/min, reduce dose to 15mg daily
		• 5 mg twice daily
		• Reduce to 2.5 mg twice daily in patients with two or more of the following characteristics:
		  ○ Age ≥80 yr
		  ○ body weight ≤ 60kg
		  ○ serum creatinine ≥1.5 mg/dL (133 micromole/L)
			• 60mg daily
			• Reduce dose to 30mg with 1 or more of following risk factors:
			  ○ Moderate to severe renal impairment,
			  ○ <=60kg,
			  ○ concomitant use of P-glycoprotein inhibitors

Dose in treatment and prevention of DVT and PE Short duration of therapy (at least 3 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.			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**

• 150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days.
• 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 75-80yrs
  ○ CrCl 30-50ml/min
  ○ Patients with gastritis, esophagitis or gastroesophageal reflux
  ○ Other patients at increased risk of bleeding
	• 15mg twice daily for days 1-21 then 20mg daily	• Treatment: 10mg twice daily for the first 7 days followed by 5mg twice daily
		• Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE: 2.5mg twice daily following 6months of treatment with 5mg twice daily or another anticoagulant
			• 60mg daily following parenteral anticoagulant for at least 5 days
			• Reduce dose to 30mg with 1 or more of following risk factors:
			  ○ Moderate to severe renal impairment,
			  ○ <=60kg,
			  ○ concomitant use of P-glycoprotein inhibitors

VTE prevention post-surgery			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
220mg once daily for: • 10days post knee surgery • 4-5weeks post hip surgery *75mg initially, then 150mg daily for: • 10 days post knee surgery • 4-5 weeks post hip surgery *For patients with: • CrCl 30-50ml/min, • Patients who receive concomitant verapamil, amiodarone, quinidine, • Patients aged 75years and above 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	10mg once daily for: • 2 weeks post knee surgery • 5 weeks post hip surgery	2.5mg twice daily for • 10-14 days post knee surgery • 32-38 days post hip surgery	Not licensed

ACS			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Not licensed	• 2.5mg twice daily with aspirin alone or aspirin + clopidogrel/ticlopidine. • Review regularly. • Extension 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

Method of administration			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
With or without food	With food	With or without food	With or without food

Unable to swallow medication			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
• Not to open the capsule as this may increase the risk of bleeding	• Tablet 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 a small amount 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	• 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 (5%dextrose in water) and immediately delivered through a nasogastric tube. • Crushed tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.	• Not stated

Missed dose (Note: short half life so decreased effect if poor compliance)			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
• May still be taken up to 6 hours prior to the next scheduled dose • No double dose should be taken to make up for missed individual doses	• Take missed dose immediately and then continue the following day with once daily intake as recommended. • Do not double within the same day to make up for a missed dose (except if taking 15mg twice daily for DVT/PE, take 30mg daily the next day. Then continue with 15mg twice daily the following day)	• Take missed dose immediately and then continue with twice daily intake as before.	• Take missed dose immediately then continue with once daily dose. Do not double the prescribed dose on the same day

Renal impairment

Renal function should be assessed prior to initiation and at least once a year or more frequently as needed in certain situations (e.g. 1-3 months) when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products). Note: In practice eGFR and CrCL are not interchangeable; however for average build and height, eGFR could provide some guidance. The SPC of each NOAC recommends that 'Cockcroft and Gault' formula is used for dosing and monitoring.

$$\text{CrCl} = \frac{[140 - \text{age (yrs)}] \times \text{ideal body weight or actual if less (kg)} \times 1.23 \text{ for males (1.04 in women)}}{\text{Serum creatinine (micromole/l)}}$$

(See BNF: Prescribing in renal impairment and electronic calculator link

	Dabigatran (Pradaxa)[1]	**Rivaroxaban (Xarelto)[2]**	**Apixaban (Eliquis)[3]**	**Edoxaban (Lixiana)[4]**
CrCl<15ml/min	Contra-indicated	Not recommended	Not recommended	Not recommended
CrCl 15-29ml/min	Contra-indicated	15mg daily	2.5mg twice daily	30mg daily
CrCl 30-49ml/min	No dosage adjustment unless bleeding risk, then reduce to 110mg twice daily	15mg daily	No dosage adjustment	30mg daily

Hepatic impairment (Hepatic disease-coagulopathy, bleeding risk inc. cirrhotic patients with Child-Pugh Score B and C)				
	Dabigatran (Pradaxa)[1]	**Rivaroxaban (Xarelto)[2]**	**Apixaban (Eliquis)[3]**	**Edoxaban (Lixiana)[4]**
Hepatic impairment	Contra-indicated where expected to have impact on survival	Contra-indicated in hepatic disease	Severe – not recommended Mild to moderate - caution	Contra-indicated in hepatic disease
Patients with elevated liver enzymes > 2 ULN	Not recommended	Not stated	Caution (inc. total bilirubin ≥ 1.5 x ULN)	Caution; LFTs prior to initiating

Drug interactions (see SPC and drug interactions table for complete list)				
	Dabigatran (Pradaxa)[1]	**Rivaroxaban (Xarelto)[2]**	**Apixaban (Eliquis)[3]**	**Edoxaban (Lixiana)[4]**
Strong CYP 3A4 and P-glycoprotein inhibitors **e.g.** ketoconazole, cyclosporin, itraconazole, tacrolimus, dronaderone	Contra-indicated	Avoid	Not recommended	Reduce to 30mg
Mild to moderate P-glycoprotein inhibitors **e.g.** amiodarone, quinidine, verapamil and ticagrelor	Caution	Not stated	No dosage adjustment	No dosage adjustment
[c]Co-administration with P-glycoprotein inducers **e.g.** rifampicin, St John's Wort, carbamazepine or phenytoin	Avoid	Avoid unless the patient is closely observed for signs and symptoms of thrombosis	Not recommended	Caution
NSAIDs	Bleeding risk may be increased (also with SSRIs and SNRIs)	Care	Care	Chronic use not recommended

Contra-indications and warnings			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
A lesion or condition, if considered a significant risk factor for major bleeding. This may include: • current or recent gastrointestinal ulceration • presence of malignant neoplasm 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 malformation • vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities Concomitant treatment with any other anticoagulant agent - e.g. unfractionated heparin, low molecular weight heparin (such as enoxaparin or dalteparin), heparin derivatives (such as fondaparinux), oral anticoagulants (such as warfarin).			

Mechanical prosthetic heart valve			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Contra-indicated	Not studied – not recommended	Not studied – not recommended	Not studied – not recommended SPC states that edoxaban may be used with bioprosthetic heart valve after first 3 months

Reversibility London medicines evaluation network			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Idarucizumab (Praxbind®) Launched December 2015. Available in UK Priced at £2,400 per dose (2 x 50g vials) – shelf life 24 months.	No antidote Andexanet alfa in phase lll studies. Expected launch 2017 Activated charcoal may be considered	No antidote Andexanet alpha in phase lll studies. Expected launch 2017 Prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered for life threatening conditions	No antidote. Aripazine in phase 2 studies with edoxaban but being developed as a universal antidote UK availability not known. 4-factor prothrombin complex concentrate (PCC) Recombinant factor VIIa (r-FVIIa) can also be considered for life threatening conditions.

Half life (t ½)[6]

Dabigatran (Pradaxa®)[1]	Rivaroxaban (Xarelto®)[2]	Apixaban (Eliquis®)[3]	Edoxaban (Lixiana®)[4]
Healthy elderly – 11 hours; multiple doses -12-14 hours. If renal impairment: **GFR (ml/min)** / **Half life (range, hours)** ≥ 80 / 13.4 (11.0-21.6) ≥ 50-< 80 / 15.3 (11.7-34.1) ≥ 30-< 50 / 18.4 (13.3-23) < 30 / 27.2(21.6-35)	• t ½ 5- 9 hours in young individuals, • t ½ of 11-13 hours in the elderly.	• Approximately 12 hours	• 10 to 14 hours

Conversion to NOAC from warfarin

Dabigatran (Pradaxa®)[1]	Rivaroxaban (Xarelto®)[2]	Apixaban (Eliquis®)[3]	Edoxaban (Lixiana®)[4]
Stop warfarin. Start dabigatran when INR <2	Discontinue warfarin and start rivaroxaban when: • INR <=3 for prevention of stroke and systemic embolism • INR <=2.5 for DVT, PE and prevention of recurrence	Discontinue warfarin and start apixaban when INR <2	Discontinue the warfarin and start edoxaban when INR is ≤ 2.5

Conversion from NOAC to warfarin			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Adjust the starting time of the warfarin based on CrCL as follows: • CrCL ≥ 50 mL/min, start warfarin 3 days before discontinuing dabigatran etexilate • CrCL ≥ 30-< 50 mL/min, start warfarin 2 days before discontinuing dabigatran etexilate As dabigatran can increase INR, the INR will better reflect warfarin's effect only dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution	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	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 apixaban. • Continue co administration of apixaban and warfarin therapy until the INR is ≥ 2.0.	60mg dose: Administer 30mg +warfarin 30mg dose: Administer 15mg + warfarin Do not take loading dose of warfarin in order to promptly achieve INR2-3. Take account of maintenance dose of warfarin and if patient was previously taking warfarin or use validated INR driven warfarin treatment algorithm. • 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

Conversion from parenteral anticoagulant to NOAC			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Discontinue the parenteral anticoagulant and start dabigatran 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH))	Discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin)	Switching treatment from parenteral anticoagulants to apixaban (and vice versa) can be done at the next scheduled dose	Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose.

Compliance aids			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
Unsuitable	No special precautions for storage	No special precautions for storage	No special precautions for storage

Cost per 28 days at usual dose (Drug Tariff August 2017)			
Dabigatran (Pradaxa®)[1]	**Rivaroxaban (Xarelto®)[2]**	**Apixaban (Eliquis®)[3]**	**Edoxaban (Lixiana®)[4]**
£47.60	£50.40	£53.20	£49.00

References

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