Primary care prescribing guidance for the use of Novel Oral anti-coagulants (NOACs) in Venous Thromboembolism (VTE)

This guidance covers the use of oral anticoagulants in line with NICE Guidelines and local services. As per NICE specification, all medicines carrying a NICE Technology Appraisal (TA) and corresponding licenced indication should be available. The treatment selection should involve a holistic approach where relevant aspects of each treatment option are discussed with the patient before initiation. This involves assessing the benefits and risks of warfarin and NOACs and allowing patient judgement to form part of the treatment decision.

The treatment of choice is tinzaparin and warfarin

Warfarin should always be considered due to the evidence base and clinical understanding. NOACs of choice are rivaroxaban and apixaban due to the lower risk of major bleeding. In addition both rivaroxaban and apixaban do not require initial treatment with a low molecular weight heparin.

The following patients may be more appropriately treatment with a NOAC

1. Patients with provoked VTE
2. Patients with fractures or assessed as high risk of clot after a fracture
3. Intravenous drug users
4. Patients allergic to warfarin
5. Patients unable to maintain INR despite best attempts to optimise treatments.
6. Patients with dosette boxes or those whose clinical situation would make treatment with warfarin difficult

Table 1: further information on NOACs (please use in conjunction with the SPC)

Medicine	**Rivaroxaban (Xarelto®)**	**Apixaban (Eloqis®)**	**Dabigatran (Pradaxa®)**	**Edoxaban (Lixiana®)**
License	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.			
Dose	Day 1-21: 15mg BD Day 21+ : 20mg OD	Day 1-7: 10mg BD Day 8+ : 5mg BD **Dose is 2.5mg BD for elderly, renal impairment or patients on long term treatment.**	150 mg BD **following** treatment with parenteral anticoagulant for at **least 5 days** **Age > 80 years should receive 110mg BD**	60mg OD **following initial** use of parenteral anticoagulant for at **least 5 days** **Patients with a weight < 60kg should receive 30mg OD**
Use in renal impairment	Avoid NOACs in patients with Creatinine Clearance (CrCL) <30ml/min due to increased risk of drug accumulation. •Patients who develop acute renal failure should discontinue the NOAC and seek specialist advice •**Creatinine clearance must be calculated** as eGFR is NOT considered a suitable alternative			
CrCl 30-50ml/min	Limited clinical data: maintenance dose may be reduced to 15 mg OD based on	No dose adjustment	Consider 110mg BD	30mg OD
CrCl 15-30ml/min		Use with caution	Contraindicated	30mg OD

	bleeding risk and risk of recurrent VTE			
Contraindications	Hypersensitivity to drug or excipients •Active clinically significant bleeding •Risk factors for major bleeding e.g. 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, venous stents. •Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. •Dabigatran is contraindicated and rivaroxaban and apixaban are not recommended in patients with prosthetic heart valves. •Pregnancy, breast feeding •Arteriovenous malformations, concomitantly with unfractionated heparin, LMWH, heparin derivatives i.e. fondaparinux or oral anticoagulants i.e. warfarin except when switching anticoagulant treatment or while receiving UFH through a venous or arterial line to keep patent. •CrCl < 15ml/min and patients receiving dialysis			

Please check latest edition of the BNF for drug interactions and cautions

Summary of anticoagulants for acute VTE and their characteristics

Indications	Heparin	Tinzaparin	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Extensive DVT or massive PE	✓						
High initial risk of bleeding	✓						
Active cancer		✓					
Pregnancy		✓					
Liver dysfunction			✓				
Limited access to anticoag.clinic				✓	✓	✓	✓
All oral therapy					✓	✓	
CrCl 30-50ml/min			✓		✓	✓	✓
CrCl < 30ml/min			✓				
Recent GI bleed			✓			✓	
Recent acute coronary syndrome					✓	✓	

Creatinine Clearance estimation tables*

Anticoagulants for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Drug use and dosing based on kidney function estimation (estimated creatinine clearance [eCrCl])

CrCl >50 ml/min	**Any anticoagulant** – no dose adjustment needed based on kidney function
CrCl 30–49 ml/min	**Apixaban** 5 mg twice daily or 2.5 mg twice daily if serum creatinine (SCr) ≥133 μmol/L with age ≥80 years or body weight ≤60 kg **Dabigatran** 110 mg twice daily if high risk of bleeding (suggest use of HAS-BLED score to assess risk); otherwise 150 mg twice daily **Rivaroxaban** 15 mg once daily **Warfarin** International normalised ratio (INR) dependent dose adjustment
CrCl 15–29 ml/min	**Apixaban** 2.5 mg twice daily **Dabigatran** contraindicated **Rivaroxaban** 15 mg once daily but caution – plasma concentrations significantly increased (average 1.6-fold), which may increase bleeding risk **Warfarin** INR dependent dose adjustment under expert advice and review
CrCl <15 ml/min	No anticoagulant use recommended in general use, take expert advice

SCr (μmol/L)	Women ≥60 kg* eCrCl (ml/min) (NB do not use table if weight <60 kg – see below) Age (years)													Men ≥70 kg* eCrCl (ml/min) (NB do not use table if weight <70 kg – see below) Age (years)												
	40	45	50	55	60	65	70	75	80	85	90	95	100	40	45	50	55	60	65	70	75	80	85	90	95	100
50	120	114	108	102	96	90	84	78	72	66	60	54	48	168	160	151	143	134	126	118	109	101	92	84	76	67
60	100	95	90	85	80	75	70	65	60	55	50	45	40	140	133	126	119	112	105	98	91	84	77	70	63	56
70	86	81	77	73	69	64	60	56	51	47	43	39	34	120	114	108	102	96	90	84	78	72	66	60	54	48
80	75	71	68	64	60	56	53	49	45	41	38	34	30	105	100	95	89	84	79	74	68	63	58	53	47	42
90	67	63	60	57	53	50	47	43	40	37	33	30	27	93	89	84	79	75	70	65	61	56	51	47	42	37
100	60	57	54	51	48	45	42	39	36	33	30	27	24	84	80	76	71	67	63	59	55	50	46	42	38	34
110	55	52	49	46	44	41	38	35	33	30	27	25	22	76	73	69	65	61	57	53	50	46	42	38	34	31
120	50	48	45	43	40	38	35	33	30	28	25	23	20	70	67	63	60	56	53	49	46	42	39	35	32	28
130	46	44	42	39	37	35	32	30	28	25	23	21	18	65	61	58	55	52	48	45	42	39	36	32	29	26
140	43	41	39	36	34	32	30	28	26	24	21	19	17	60	57	54	51	48	45	42	39	36	33	30	27	24
150	40	38	36	34	32	30	28	26	24	22	20	18	16	56	53	50	48	45	42	39	36	34	31	28	25	22
160	38	36	34	32	30	28	26	24	23	21	19	17	15	53	50	47	45	42	39	37	34	32	29	26	24	21
170	35	34	32	30	28	26	25	23	21	19	18	16	14	49	47	44	42	40	37	35	32	30	27	25	22	20
180	33	32	30	28	27	25	23	22	20	18	17	15	13	47	44	42	40	37	35	33	30	28	26	23	21	19
190	32	30	28	27	25	24	22	21	19	17	16	14	13	44	42	40	38	35	33	31	29	27	24	22	20	18
200	30	29	27	26	24	23	21	20	18	17	15	14	12	42	40	38	36	34	32	29	27	25	23	21	19	17

Current evidence suggests that an absolute CrCl (Cockcroft & Gault), as used in drug licence dosing studies, should be used for dosing decisions, not normalised estimated glomerular filtration rate (eGFR), especially for older patients and for narrow therapeutic index and high-risk drugs.

The tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights when eCrCl should be calculated individually (manually using the Cockcroft & Gault equation in **Box 2** or on e.g. SystmOne>clinical tools>renal calculations) *Average ideal body weight.

Based on data taken from the current Summaries of Product Characteristics (SmPCs). Available from: www.medicines.org.uk/emc/

Box 2. The Cockcroft & Gault equation(17)

$$\text{Creatinine clearance} = \frac{(140 - \text{age [years]}) \times \text{ideal body weight or actual if less (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})} \times 1.2 \text{ for males}$$

*Ref: Wood W, Petty D, Assessing kidney function in oral anticoagulant prescribing: an aid for safer drug and dose choices. **June 2013Br J Cardiol 2013;20:61–4**