



North Central London
Joint Formulary Committee

NCL DOAC Prescribing Guidelines (adults)

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Document control

Date	Version	Amendments
20Dec16	1	New document
20Apr18	1.1	DOAC Initiation Checklist – Platelet threshold to trigger discussion with Haematologist before initiation has been changed. It now recommends discuss with Haematologist if platelet count < 100 x 10 ⁹ /L. Frequency of monitoring brought into line with EHRA 2018 guideline
September 2022	2.0	Document reviewed and updated

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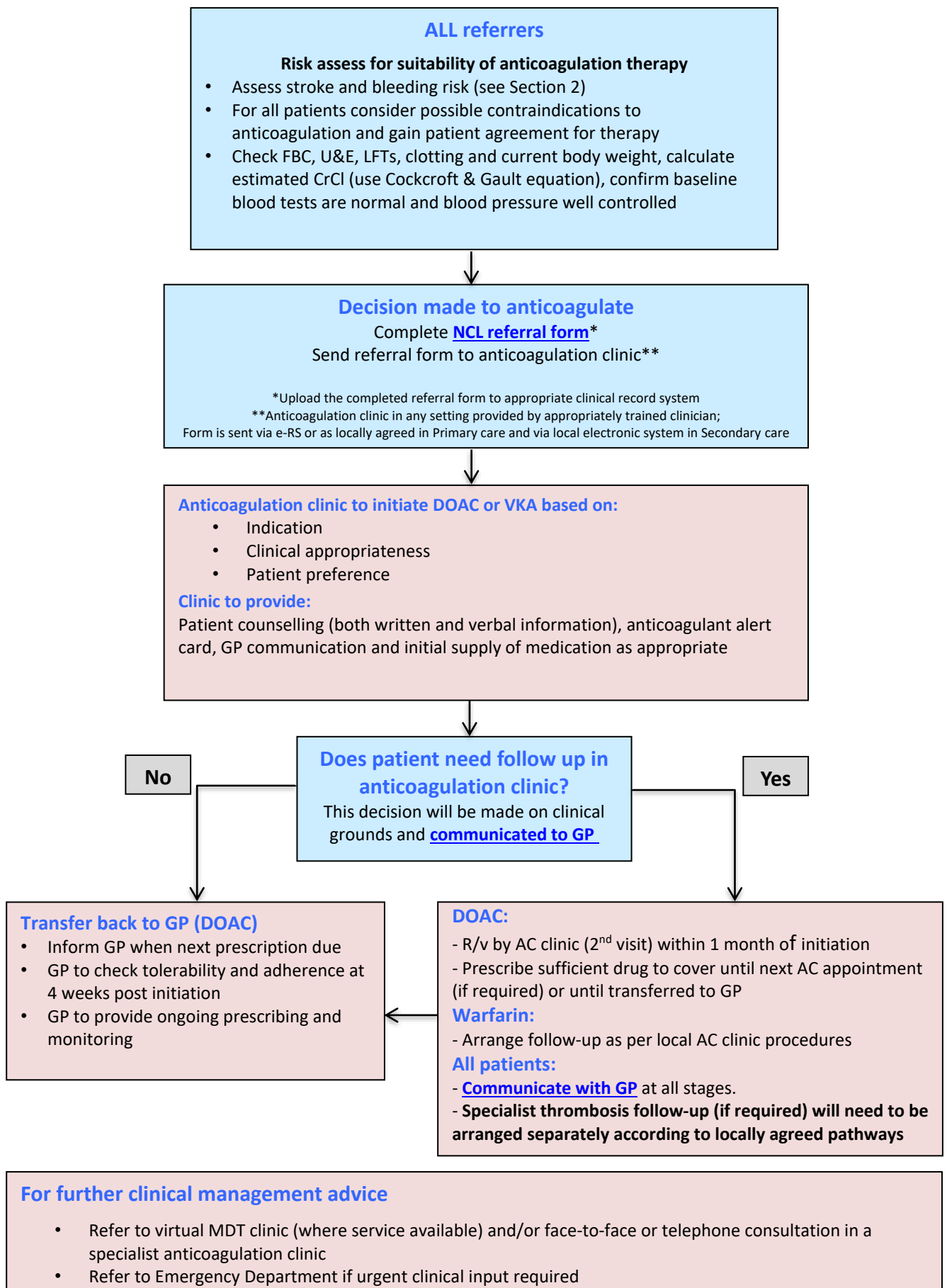
Definitions

“Anticoagulation clinic” - refers to the clinic in any setting provided by an appropriately trained clinician

“MHRA” – Medicines and Healthcare Regulatory Agency

“Creatinine clearance” – A test that measures the ability of the kidney to eliminate creatinine from the body. It is sometimes abbreviated to “CrCl”. See [Section 10](#) for information on how to calculate.

1. Clinic referral for initiation of anticoagulation (for prescribers who do not provide an anticoagulation service)



2. Assessing stroke/bleeding risk for patients with non-valvular AF¹⁻³

Tool to assess stroke risk		Bleeding risk tools (use either HAS-BLED or ORBIT) †			
CHA ₂ DS ₂ Vasc	Score	HAS-BLED	Score	ORBIT	Score
Congestive heart failure/ LV dysfunction	1	Hypertension (uncontrolled, > 160mmHg systolic)	1	Men: Haemoglobin <130g/L or haematocrit <40% Women: Haemoglobin <120g/L or haematocrit <36%	2
Hypertension history	1	Chronic liver disease or bilirubin 2xULN with AST/ALT/ALP 3x ULN	1		
Age ≥75	2	Abnormal renal function (creatinine ≥200µmol/L, CrCl < 50ml/min, renal transplant, or chronic dialysis)	1	Age >74 years	1
Diabetes Mellitus history	1	Ischaemic or haemorrhagic stroke	1	Bleeding History (Any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke)	2
Stroke/TIA/Systemic arterial embolism	2	History of major bleeding‡ or predisposition	1		
Vascular disease (previous MI, peripheral arterial disease, aortic plaque)	1	Labile INRs, time in range of 2-3 less than 60%	1	GFR <60ml/min/1.73m ²	1
Age 65 to 74	1	Elderly (age ≥65 or frail condition)	1	Treatment with antiplatelet agents	1
Sex (male 0, female 1)	F 1	Drugs (concomitant antiplatelet, NSAIDs etc.) or alcohol use ≥ 8 units/week (1 point each)	1 or 2		
Total score (Maximum score 9)		Total score (Maximum score 9)		Total score (Maximum score 7)	

† NICE recommends the use of ORBIT for patients with atrial fibrillation

‡ Bleeding requiring hospitalisation and/or causing decrease in Hb >20g/L and/or requiring ≥2 units blood transfusion.

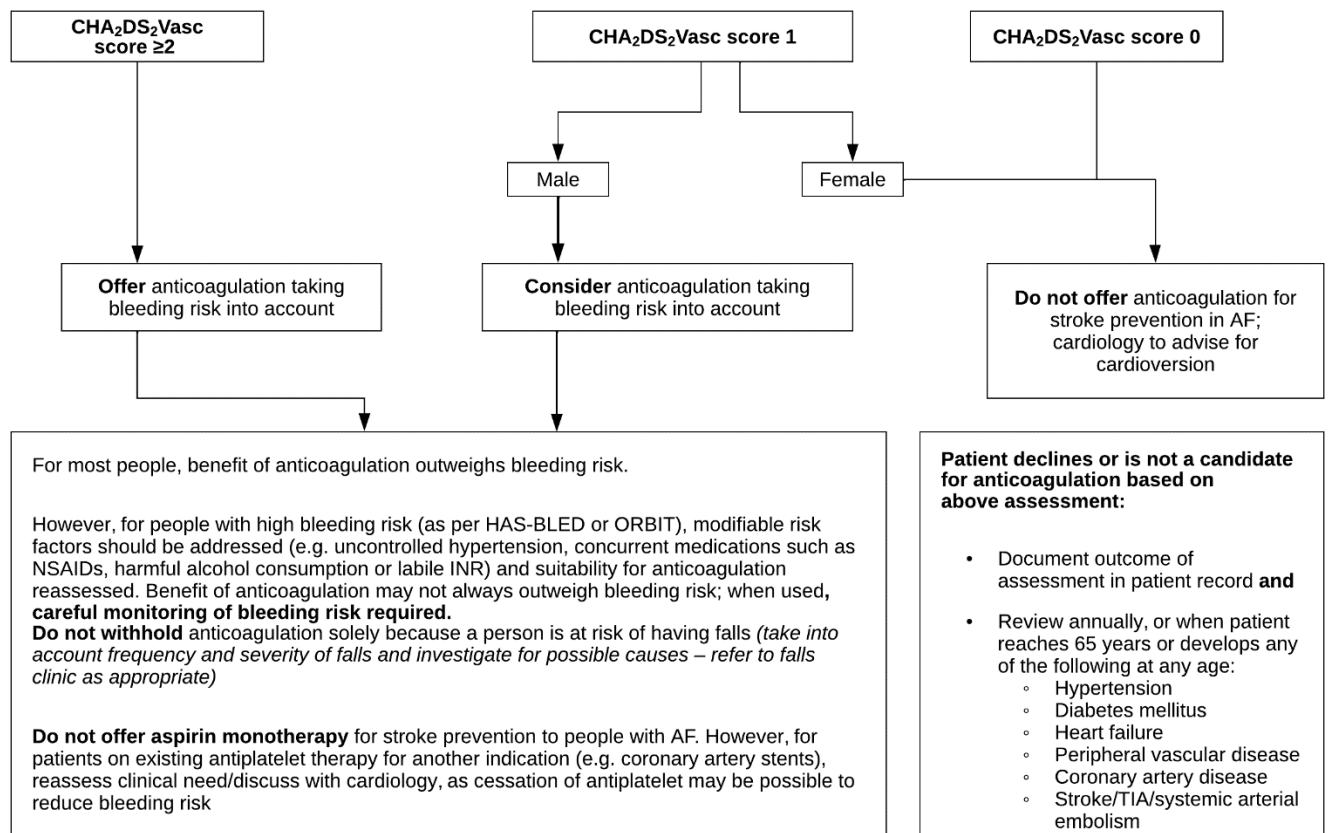
Stroke and bleed risk⁴⁻⁶

CHA ₂ DS ₂ Vasc Score	Risk of stroke/ TIA/ systemic embolism (%/year)
0	0.3%
1	0.9%
2	2.9%
3	4.6%
4	6.7%
5	10.0%
6	13.6%
9	17.4%

HAS-BLED Score	Major bleed per 100 patient years	Risk group
0	1.13	Relatively low
1	1.02	
2	1.8	Moderate
3	3.74	High
4	8.70	
5	12.50	
6-9	Insufficient data	Very high

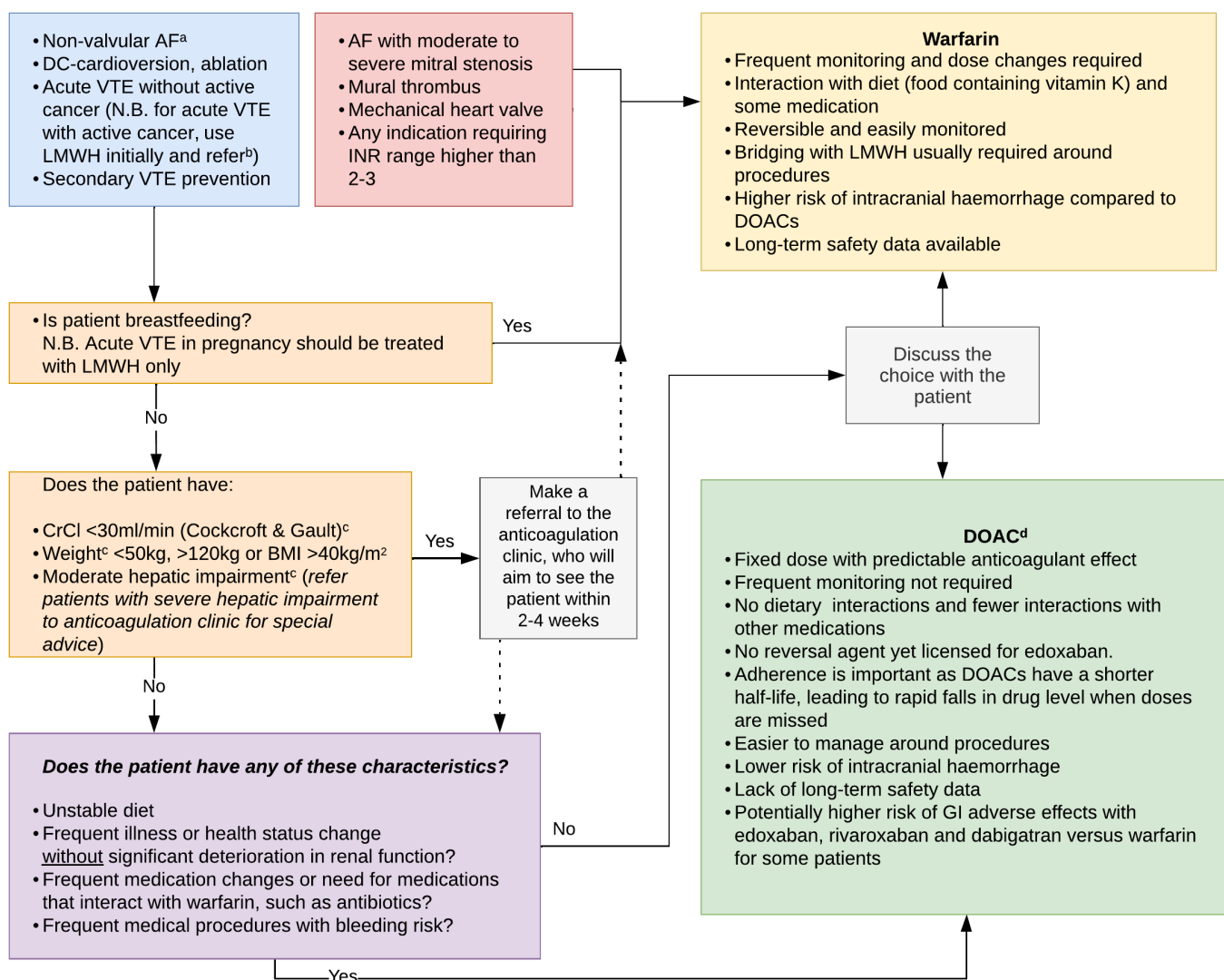
ORBIT Score	Major bleed per 100 patient years	Risk group
0 - 2	2.4	Low
3	4.7	Medium
4-7	8.1	High

Decision support tool for anticoagulating patients with non-valvular AF



3. Anticoagulant Selection Tool - guide⁷

Flow chart adapted from toolkit produced by Michigan Quality Improvement Initiative



- Non-valvular AF refers to AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin).⁸
- Initiate with LMWH and refer to local VTE oncology clinic / discuss with local haematology consultant for consideration of a DOAC. DOACs were approved for use in NCL patients with active cancer (see [JFC May 2022 minutes](#)).
- Patients with CrCl <30mL/min were excluded from clinical trials (CrCl <25mL/min for apixaban). DOACs are considered after review in an anticoagulation clinic. Patients with ALT/AST 2xULN (ALT 3xULN for rivaroxaban) or bilirubin \geq 1.5xULN were excluded from the main clinical trials; DOACs are either contraindicated or are to be used cautiously depending on degree of liver impairment (refer to SmPC).⁹ Limited data at extremes of body weight – discuss with haematologist before use; Each DOAC is only approved for certain indications and may have warnings for use in specific populations (i.e. renal impairment/hepatic failure) and with certain concurrent medications (P-gp/CYP3A4 inducers or inhibitors).

4. Choice of oral anticoagulant based on patient characteristics^{7,8,10,11}

Patient characteristic	Drug choice	Rationale / comment
Mechanical heart valve	Warfarin	Increased risk of thrombosis/bleeding with dabigatran compared to warfarin (former contraindicated); other DOACs not studied in this setting
AF with valvular disease ^a	Warfarin	DOAC trials excluded patients with mechanical valves, moderate to severe or haemodynamically significant mitral stenosis
Any indication requiring higher range INR than 2-3	Warfarin	DOAC AF and VTE trials were compared against warfarin with target INR range 2-3
Moderate hepatic impairment (Child-Pugh B)	Refer to anticoagulation clinic for assessment	Patients with ALT/AST 2 x ULN (ALT 3 x ULN for rivaroxaban) or Bili \geq 1.5 x ULN were excluded from the main clinical trials. Use of DOACs in patients with moderate hepatic impairment is not recommended (see individual SmPC's for further details)
Severe hepatic impairment (Child-Pugh C)	Refer to anticoagulation clinic for assessment	All DOACs are contraindicated in patients with severe hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients (refer to SmPC)
CrCl <30 mL/min	Refer to anticoagulation clinic for assessment	Patients with CrCl <30mL/min were excluded from clinical trials (CrCl <25mL/min for apixaban). NCL currently advises against the routine use of DOAC in severe renal impairment unless discussed with a Haematologist. (For CrCl 15-29ml/min, AUC increases by 44%, 72% and 1.6 fold for apixaban, edoxaban and rivaroxaban respectively NB: dabigatran contraindicated with CrCl < 30mL/min; apixaban, edoxaban and rivaroxaban should not be used if CrCl; < 15ml/min. ¹³⁻¹⁶
Extremes of body weight <50 kg or >120 kg (or BMI >40kg/m ²)	Refer to anticoagulation clinic for assessment	Routine use of DOACs not advised (local recommendation) unless discussed with the anticoagulation service (limited data at extremes of body weight) ^b .
Antiphospholipid syndrome	Haematologist to advise	Haematology consultant to advise on anticoagulation management in accordance with national and international guidance ¹⁷⁻¹⁹ and following EMA recommendations ²⁰ and MHRA drug safety update ²¹
Previous intracranial bleed (Decision to anticoagulate as per neurosurgical advice)	Haematologist/ Stroke physician to advise	Risk of intracranial bleeding less with DOACs than Warfarin. Patients with previous intracranial bleed excluded from trials. ^{22,23}
AF associated with acute ischaemic stroke	Stroke physician to advise	The choice of anticoagulant agent and start time is patient specific.
Indication for dual antiplatelet therapy (e.g., elective PCI, PCI post ACS)	Refer to Cardiologist	Individualised patient approach is needed and is dependent on thrombosis vs bleeding risk. Dual antiplatelet therapy (DAPT) is necessary to prevent stent thrombosis but not sufficient for stroke prevention; short term triple-therapy (warfarin or DOAC with DAPT) may be indicated. Minimal duration on triple therapy (if appropriate) should be aimed for. In all cases, a management plan should be discussed with the cardiologist.

^a Valvular AF generally refers to AF in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve.¹²

Patient characteristic	Drug choice	Rationale / comment
Patients with VTE in active cancer	LMWH initially, then refer to haematology; Apixaban Rivaroxaban	DOACs were approved for use in patients with active cancer (see JFC May 2022 minutes) and NICE guidance . Initiation of DOAC is by a haematologist in line with local guidance after considering tumour site, potential cautions and contraindications (including interactions with cancer therapy) and the individual's bleeding risk. Treatment duration is at least 3 to 6 months, and some patients may require long-term prevention (particularly after an unprovoked VTE). ²⁴
Patients indicated for anticoagulation and undergoing bariatric surgery (gastric-bypass, lap band surgery, or gastrectomy) ²²	LMWH in post-op setting initially	Scant literature is available on the effects of bariatric surgery on post-op oral anticoagulation of DOACs. Drug bioavailability can be unpredictable and depends on numerous factors (e.g., food intake, GI absorptive surface, location of drug absorption, GI transit time etc.). Note also limited clinical data with DOAC in body weight >120kg or BMI >40 kg/m ² . ⁹ Where anticoagulation is indicated, advise use of LMWH for at least 4 weeks post-op before considering oral AC therapy; patient should be referred to patient's local AC clinic to review choice; warfarin may be the optimal AC choice longer-term. If DOAC used, this should be via Specialist AC clinic and specific DOAC monitoring advised ⁹
CrCl >95ml/min	Warfarin, Apixaban Rivaroxaban, Dabigatran	Stroke prevention in NVAf: Trend towards decreasing efficacy of edoxaban with increasing CrCl, compared to well-managed warfarin. SmPC for edoxaban cautions use with high CrCl (Note: prescribing information in the United States advises edoxaban should not be used in NVAf if CrCl > 95ml/min ²⁵
Dyspepsia or history of gastrointestinal bleeding/ulcer (Check that underlying cause has been treated)	Warfarin, Apixaban	Dabigatran can cause dyspepsia Higher GI bleed risk with dabigatran (150mg), edoxaban (60mg) or rivaroxaban than with warfarin; no difference in GI bleed risk with apixaban vs warfarin (AF studies) ²⁶⁻²⁸ . Likely to also apply to VTE patients. Warfarin is easier to reverse if there is a bleed. ²⁶⁻²⁸
Patients receiving rivaroxaban and aspirin for peripheral arterial disease/ coronary artery disease	See information	There is a NICE TA to support the use of a low dose rivaroxaban (2.5mg), used together with aspirin, for the prevention of atherothrombotic events in patients with PAD/CAD (see NICE TA607 or NCL antiplatelets guideline for more information). Rivaroxaban 2.5mg should not be used in patients with atrial fibrillation; discuss with the secondary care anticoagulation service for advice
Swallowing difficulties / feeding tubes	Warfarin, Apixaban, Edoxaban, Rivaroxaban	DOACs must not be administered via jejunal tubes. ²⁹ Apixaban can be crushed and mixed with water, 5% glucose in water, apple juice or apple puree prior to oral administration, or mixed with water or 5% glucose in water prior to immediate delivery via nasogastric administration (other gastric tube administration is off-label). ¹⁴ Rivaroxaban and edoxaban are both licensed to be crushed and mixed with water or apple puree prior to oral administration or crushed and mixed with water prior to gastric tube administration. Tablets are stable for up to 4 hours in water or apple puree. ^{13,15} Rivaroxaban 15mg or 20mg tablets should be immediately followed by food or enteral feed, to maximize bioavailability. ²⁹ Dabigatran must not be used for patients with swallowing issues and the capsules must not be opened; this increases the bioavailability and risk of bleeding¹⁶ Warfarin tablets can be crushed, mixed with water and administered via gastric or jejunal tubes (off-label); warfarin suspension is available. Enteral feeds should be stopped 1-2 hours before and re-started 1-2 hours after each dose. Monitor INR closely if route of administration is changed. ²⁹
Requirement for compliance aid such as blister pack/'dosette box'	Rivaroxaban, Apixaban, Edoxaban	Dabigatran capsules must be kept in their original container. ¹⁶ Warfarin should not be dispensed into a sealed compliance aid (due to variable dosing and hence safety reasons).

5. DOAC preference in NCL

Venous thromboembolism

- **Rivaroxaban** is the preferred DOAC in NCL for the treatment of acute VTE where clinically appropriate
- **Apixaban** is considered for use:
 - In individuals with a high risk of mucosal bleed; or
 - where compliance of taking rivaroxaban with food cannot be assured (but twice daily apixaban can be assured).

Non-valvular atrial fibrillation

- **Edoxaban** is the preferred DOAC in NCL for new initiations in NVAF where clinically appropriate
- **Rivaroxaban** is considered for use:
 - In patients with a CrCl (Cockcroft & Gault) >95ml/min
 - Where drug interactions preclude the use of edoxaban
- **Apixaban** is considered for use:
 - In the frail/elderly/patients with low body weight and/or renal impairment
 - For individuals at high risk of GI or mucosal bleeding
 - Where potential drug interactions preclude the use of edoxaban or rivaroxaban
- Patients in primary care already receiving **Rivaroxaban*** for NVAF may be considered for a switch to edoxaban, unless they have one or more high risk exclusion criteria, including:
 - Where cautions/contraindications or drug interactions preclude the use of edoxaban
 - Where a specialist has indicated the clinical reason for using an oral anticoagulant other than edoxaban
 - In patients with a CrCl (Cockcroft & Gault) >95ml/min
 - Patients with BMI >40 or weight >120kg
 - Active malignancy or chemotherapy (and where rivaroxaban is appropriate to continue)
 - Cognitive dysfunction (e.g., concerns around the patient's understanding)

(*patients taking **apixaban** should not be considered for primary care switching)

Further information can be found in the relevant NCL position statement:

- [NCL position statement: Choice of DOAC in venous thromboembolism](#)
- [NCL position statement: Choice of DOAC in non-valvular atrial fibrillation](#)

6. DOAC initiation checklist

Checklist	Comments
Counsel the patient on DOAC initiation	Refer to the DOAC counselling checklist
<p>Assess bleeding risk:</p> <ul style="list-style-type: none"> • HASBLED / ORBIT score – alcohol consumption should not exceed nationally recommended amount (address risk factors for bleeding where possible) • Check for lesions or conditions considered to be significant risk factors for major bleeding • Frequency and severity of falls • Check FBC and clotting, (<i>last 4 weeks</i>) 	<p><u>Patients with the following conditions should be discussed with a Haematologist or other specialist as appropriate:</u></p> <ul style="list-style-type: none"> • Current/recent upper or lower GI ulceration, oesophageal varices (known or suspected), malignant neoplasms at high risk of bleeding • Surgery/trauma/bleed affecting head/brain, eyes or spine within last 4 weeks • AV malformations, vascular aneurysms or major intraspinal/intracerebral vascular abnormalities • Thrombocytopenia (platelets $<100 \times 10^9/L$) • Congenital or acquired bleeding disorder (abnormal baseline clotting screen, haemophilia, low fibrinogen) • Post stroke: Optimal time to commence AC after acute ischaemic stroke associated with AF is unknown. Usually, AC is commenced within 2 weeks of symptom onset and should be discussed with a stroke consultant before initiation.
<p>Ensure DOAC use is licensed for required indication</p> <p>Examples of licensed indications</p>	<ul style="list-style-type: none"> • DOACs are currently only approved for stroke prevention in patients with non-valvular atrial fibrillation and treatment/prevention of VTE (DOACs are contraindicated in patients with mechanical heart valves and should not be used for indications requiring higher intensity anticoagulation e.g., INR target greater than 2.5 (range higher than 2.0 – 3.0) if on warfarin)
<p>Haematologist/stroke physician to advise on anticoagulation for patients with:</p>	<ul style="list-style-type: none"> • Myeloproliferative disorders, nephrotic syndrome, sickle cell disease (limited evidence) • Antiphospholipid syndrome – (See Section 4) • Cerebral venous sinus thrombosis • Acute ischaemic stroke
<p>Establish length of anticoagulation based on indication^{30,31}</p>	<ul style="list-style-type: none"> • See Anticoagulation clinic referral form
<p>Check full blood count and coagulation screen (<i>last 4 weeks</i>)</p>	Check haemoglobin, platelet count and INR; if platelets (platelets $<100 \times 10^9/L$), unstable haemoglobin or INR >1.3 , discuss with haematologist
<p>Check renal function (<i>last 4 weeks</i>) (CrCl $>30\text{mL}/\text{min}$) using Cockcroft & Gault (C&G) formula</p>	DOACs rely on renal function for elimination and should be used with caution in patients with significant renal disease. DOAC dosing is adjusted according to renal function. Patients with CrCl $<30\text{mL}/\text{min}$ should be referred to the anticoagulation clinic
<p>Check liver function (<i>last 4 weeks</i>)</p>	DOACs are contraindicated in patients with significant hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (patients with ALT/AST $2 \times \text{ULN}$ or Bilirubin $> 1.5 \times \text{ULN}$ were excluded from the main clinical trials).
<p>Check blood pressure control</p>	Good blood pressure control should be achieved before initiating anticoagulation.
<p>Check body weight</p>	There is limited evidence in patients at the extremes of body weight ($< 50 \text{ kg}$, $>120 \text{ kg}$ or BMI $> 40\text{kg}/\text{m}^2$) – refer to the anticoagulation clinic (local recommendation)
<p>Review medication for potential drug interactions</p>	Some medications may increase or decrease drug exposure of DOACs and require dose adjustment as per SPC or have an additive effect on the risk of bleeding (e.g., concurrent unavoidable use of an antiplatelet agent). Consider addition of proton pump inhibitor if it is essential for patient to remain on medication that increases GI bleed risk and opt for a DOAC with lower risk of GI bleed
<p>Consider patient's compliance with medication</p>	<p>Since DOACs have a short half-life compared to warfarin and do not require monitoring, compliance may be a more important concern. Ensure the patient is aware of the importance of not missing any doses.</p> <p>Note that dabigatran must not be dispensed into reminder devices (see above).</p>
<p>Pregnancy test for women of childbearing age – advise on reliable contraception</p>	DOACs are contraindicated in pregnancy and breastfeeding (crosses placenta and into breast milk). If patient is pregnant, urgently discuss with Haematologist; if planning pregnancy, refer to Haematologist for advice regarding an alternative.

7. Switching from an anticoagulant to DOAC

- Switching should only be undertaken by clinicians in Primary or Secondary care with experience in managing anticoagulation.

7.1. Switching from warfarin to DOAC

- Discuss with the patient's anticoagulation clinic before switching from warfarin to DOAC, as this may not be appropriate in all cases (please follow the decision making tool in Section 3).
- Baseline bloods (taken within the last four weeks) are required for a switch to a DOAC (outlined in [Section 9](#))
- DOAC SmPC's recommend different INR levels for initiating DOAC after stopping warfarin; this would require repeat INR checks until the required INR is achieved.
- A more pragmatic approach on when to start DOACs after stopping warfarin, would be as follows (based on EHRA guidance, and not the individual SmPC's¹⁰), based on INR readings taken on the same day³²:
 - If INR ≤ 2 : Commence DOAC
 - If INR between 2 and 2.5: no warfarin that day and commence DOAC the next day
 - If INR between 2.5 and 3: miss 2 or 3 doses of warfarin and start DOAC
 - If INR ≥ 3 : miss 2 or 3 doses of warfarin, recheck INR and then as above.

7.2. Switching from a DOAC or LMWH to another DOAC (assuming CrCl > 30ml/min)

- If LMWH / other DOAC dosing is once daily, give the first dose of appropriate DOAC 24 hours after the last dose of LMWH / other DOAC.
- If LMWH / other DOAC is twice daily, give the first dose of appropriate DOAC 12 hours after the last dose of LMWH / other DOAC
- Do not 'cross-cover' LMWH / other DOAC with appropriate DOAC

8. DOAC dosing^{24,32}

The MHRA states that for DOACs, creatinine clearance should be calculated using the Cockcroft-Gault formula and should be used for dosing and not eGFR. See [Section 11](#) for more details.

DOAC	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
<p>Dosing in non-valvular AF</p> <p>Assumes: CrCl ≥ 30ml/min Weight ≥ 50kg - ≤ 120kg</p>	<p>20mg once daily with food</p> <p>Reduce dose to 15mg once daily with food if CrCl 30-49 mL/min (NVAf patients only)</p>	<p>5mg twice daily</p> <p>Reduce dose to 2.5mg twice daily if at least two of the following characteristics: serum creatinine ≥ 133 micromol/l (NCL specialists consider this to be approximately CrCl 30-49ml/min[†]); age ≥ 80 years; body weight ≤ 60 kg</p>	<p>60mg once daily</p> <p>Reduce dose to 30mg once daily if any of: Body weight ≤ 60kg, or CrCl 30 to ≤ 50ml/min, or co-prescribed with the p-gp inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole.</p> <p>(Note: Avoid if CrCl >95ml/min)</p>	<p>Dabigatran 150mg twice daily</p> <p>Reduce dose to 110mg twice daily if aged ≥ 80 years or if taking verapamil</p> <p>Consider 110mg twice daily if any of: age 75 – 80 years, or CrCl 30-50ml/min or history of gastritis, oesophagitis / gastroesophageal reflux, or at increased risk of bleeding (dose depends on thromboembolic vs bleeding risk)</p>
<p>Note: In patients with a high bleeding risk a reduced dose of DOAC is sometimes considered on an individual patient basis. This is off-label and without RCT outcome data.</p>				
<p>Dosing in acute DVT/PE</p> <p>Assumes: CrCl ≥ 30ml/min, Weight ≥ 50kg and ≤ 120kg</p>	<p>Initiation: 15mg BD with food for 21 days then 20mg OD with food Confirm intended duration of therapy.</p> <p>Dose adjustment for maintenance phase: If CrCl 30 to 49ml/min, consider 15mg OD if the risks of bleeding outweigh the risks of recurrent VTE <i>(NB: dose based on PK modelling and not clinical trial data)</i></p> <p>Secondary prevention of VTE recurrence: consider 10mg daily long-term.</p>	<p>Initiation: 10mg BD for 7 days Then 5mg BD Confirm intended duration of therapy</p> <p>Secondary prevention of VTE recurrence: consider 2.5mg BD long-term.</p>	<p>Initiation (NB: not first line DOAC for treatment of acute VTE within NCL): Therapeutic LMWH dose for at least 5 days. Then: 60mg once daily Confirm intended duration of therapy</p> <p>Reduce dose to 30mg once daily if: Body weight ≤ 60kg, or CrCl 30 to ≤ 50ml/min, or co-prescribed with the p-gp inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole.</p>	<p><i>(Do not use dabigatran for the treatment of acute VTE unless advised by haematology)</i></p> <p>Initiation: Therapeutic LMWH dose for at least 5 days. Then: as per dosing in AF above. Confirm intended duration of therapy.</p>

DOAC	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Duration of therapy for DVT/PE	Duration of anticoagulation recommended by secondary care anticoagulation clinic in discussion with thrombosis specialist (do not stop treatment unless advised). Typical durations include: <ul style="list-style-type: none"> 1st episode of provoked proximal DVT/PE: at least 3 months treatment if provoking factors have been addressed. Calf vein DVT: 3 months For unprovoked DVT/PE or recurrent DVT/PE: At least 3-6 months treatment dose followed by prophylactic dose as indicated/advised by haematology. 			
Creatinine clearance 15-29ml/min	Primary care: Refer to anticoagulation clinic for assessment Secondary care: Follow local pathways			Contra-indicated
Creatinine clearance <15ml/min	Contra-indicated	Contra-indicated	Contra-indicated	Contra-indicated
Extremes of body weight (<50kg or >120kg)	Primary care: Refer to anticoagulation clinic for assessment Secondary care: Follow local pathways		Do not use*	Do not use*
Pathway(s) relevant for drug interactions	P-gp substrate; CYP3A4	P-gp substrate; CYP3A4	P-gp substrate (<10% metabolised by CYP3A4)	P-gp substrate
Cautions	Must be taken with or after food (bioavailability only 66% when taken on an empty stomach)	-	Avoid if CrCl >95mL/min (trend to ↑rate of ischaemic stroke vs warfarin (AF)).	Do not open capsules (significantly increased bioavailability) Do not dispense into a standard medicine compliance aid (i.e., dosette box)
Interactions This list is not exhaustive. Please see relevant SPCs BNF: www.bnf.org Check relevant SPC via eMC website:	<u>Avoid:</u> Rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort, dronedarone and other strong CYP3A4 inducers. <u>Not recommended:</u> ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (e.g., ritonavir) (or other strong inhibitors of both CYP3A4 and P-	<u>NCL advises to avoid use (unless discussed with haematology) with:</u> rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort or other strong inducers of CYP3A4 or P-gp (refer to SPC for further information) <u>Not recommended:</u> ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (e.g., ritonavir) or other	<u>NCL advises to avoid use (unless discussed with haematology) with:</u> rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort. <u>Avoid</u> with long-term macrolides (i.e., >1 week). For longer macrolide courses, opt for rivaroxaban/apixaban. <u>Avoid if possible:</u> Clarithromycin /azithromycin; <u>caution</u> with short	Contraindicated: strong p-gp inhibitors such as ketoconazole, ciclosporin, itraconazole, dronedarone and fixed dose glecaprevir/pibrentasvir; refer to SPC for further information) <u>Avoid:</u> rifampicin, St John's Wort, carbamazepine, phenytoin. <u>Not recommended:</u> tacrolimus, protease inhibitors (e.g., ritonavir)

DOAC	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Link here	gp); refer to SPC for further details) Increased risk of bleeding with antiplatelets (use only if essential), SSRIs, SNRIs, steroids etc. Avoid NSAIDs	strong inhibitors of both CYP3A4 and P-gp; refer to SPC for further details). Increased risk of bleeding with antiplatelets (use only if essential), SSRIs, SNRIs, steroids etc. Avoid NSAIDs	courses (1 week or less) as potential to increase edoxaban plasma concentrations, especially with renal impairment <u>Reduce dose as above with:</u> ciclosporin, dronedarone, erythromycin, ketoconazole; refer to SPC. Interaction with other strong p-gp inhibitors such as itraconazole likely, based on interaction with dabigatran (though has not been studied) – discuss with local anticoagulation service Increased risk of bleeding with antiplatelets (use only if essential), SSRIs, SNRIs, steroids etc. Avoid NSAIDs	Use with caution: amiodarone, verapamil (reduce dose), quinidine, ticagrelor, clarithromycin, posaconazole; refer to SPC Increased risk of bleeding with antiplatelets (use only if essential), SSRIs, SNRIs, steroids etc. Avoid NSAIDs

* Unless specifically advised by local Haematology consultant or AC service in secondary care. Haematologist may advise individualised doses other than those detailed within these tables

† Locally, specialists tend to use CrCl 30-49ml/min as serum creatinine used in isolation may not be an accurate indicator of renal function

9. DOAC pre-initiation checks and ongoing monitoring

- DOACs are predominantly eliminated by the renal route, it is therefore prudent to regularly monitor renal function and adjust dosing accordingly.
- The renal function must be assessed using **creatinine clearance (CrCl), calculated** by the **Cockcroft Gault formula** (See [Section 11](#)). Do not use eGFR.
- **All patients require a review at least once a year by their Primary care team to ensure appropriateness of ongoing anticoagulation.**

Baseline blood tests					
Patient group	U/Es (use CrCl)	Weight	FBC	LFTs	Clotting screen
All patients	✓	✓	✓	✓	✓
Frequency of follow-up blood tests - guidance					
GP's discretion to monitor more closely where parameters fluctuate / dose is borderline for adjustment etc.					
Patient group	U/Es (use CrCl)	Weight	FBC ^b	LFTs	Clotting screen ^c
CrCl >60 mL/min	Annually ^a	Annually	Annually ^a	At least annually or more frequently during illness affecting liver function Seek advice if AST/ALT >2x or bilirubin >1.5x ULN	APPT, PT and INR will not provide information on intensity of anticoagulation effect ^c
Any of the following: Age ≥75; frail; CrCl 40-60 mL/min; weight 55-60kg	6 monthly	6 monthly	6 monthly ^b		
Any of the following: High bleeding risk; CrCl 30-40 mL/min; deterioration or fluctuation in renal function (see below*); weight < 55kg or unstable and falling	at least 3 monthly	at least 3 monthly	at least 3 monthly ^b		
CrCl <30 ml/min	<ul style="list-style-type: none"> • Dabigatran: Contraindicated • Apixaban, edoxaban, rivaroxaban: NCL guidance is not to use, unless advised by anticoagulation clinic 				
Cr CL <15 ml/min	<ul style="list-style-type: none"> • Apixaban, edoxaban, rivaroxaban: Do not use (dabigatran contraindicated if CrCl <30) 				
^a if edoxaban is used for AF, review choice of agent if CrCl >95 mL/min as reduced efficacy for stroke prevention ^b in addition to general clinical surveillance, laboratory testing of haemoglobin could be of value to detect occult bleeding, especially in patients at higher risk of bleeding complications ^c routine monitoring of anticoagulant effect of DOACs is not required. Standard coagulation parameters (APTT, PT, INR) may be affected to varying degrees by the different DOACs, but will not provide quantitative information on the level of anticoagulation achieved (poor correlation)					
*Managing deterioration of renal function					
Any acute illness or change in medication that MAY affect renal function	Check U/Es and calculate CrCl (not eGFR). Reduce dose or withhold treatment if required. Consider seeking specialist advice regarding restarting treatment.				
Significant reduction in renal function	Reduce dose as appropriate (see dosing guidance), increase frequency of routine follow-ups. Close monitoring will be required during any intercurrent illness and perioperatively. If renal function continues to worsen seek specialist advice.				
Fall of CrCl to <30mL/min	Stop DOAC, assess for bleeding and seek specialist advice as to whether specific assays are indicated/alternative anticoagulation required (i.e., switch to warfarin).				

10. Routine follow-up checklist for DOAC patients (every visit)

At each follow-up visit:	Comments
Assess compliance	<ul style="list-style-type: none"> Review prescribing schedule, calculate and document average adherence If patient has stopped taking DOAC, establish whether this was secondary to side-effects, accidental stoppage, temporary/permanent cessation by another clinician. Re-educate on importance of strict intake schedule Inform about compliance aids (e.g., dosette box, blister pack, reminder charts, smartphone applications) NOTE: Dabigatran must remain in original packaging
Assess for thrombotic complications	<ul style="list-style-type: none"> History of stroke/TIA, DVT/PE in last treatment interval
Assess for bleeding complications	<ul style="list-style-type: none"> Repeat HASBLED / ORBIT score. If at increased bleeding risk: <ul style="list-style-type: none"> Correct potentially reversible risk factors Ensure more frequent reviews are in place Check for any bleeding episodes “Nuisance bleeding” – are preventative measures possible? Reinforce importance of carrying ‘patient alert’ card at all times Reiterate standard anticoagulant advice for serious trauma, especially head injuries
Assess for other side-effects	<ul style="list-style-type: none"> Dyspepsia common with dabigatran; consider PPI or alternative agent Other side effects: Assess for possible link to DOAC. Review dose? Consider an alternative agent? Temporarily stop? <i>All adverse drug events must be reported to MHRA via the Yellow Card website</i>
Assess risk versus benefit of anticoagulation and decide whether ongoing anticoagulation is still appropriate.	
Ensure that current dose of DOAC is still optimal in light of age, weight and renal function, liver function etc.	<ul style="list-style-type: none"> See guidance on DOAC dosing in AF/VTE NCL guidance: avoid use of DOACs if CrCl <30 mL/min (dabigatran contraindicated) and/or weight is <50 kg or >120kg (BMI > 40) unless otherwise advised by haematology. If edoxaban is used for AF, review choice of agent if CrCl >95mL/min as efficacy likely reduced
Review concurrent medication, including over the counter medication, herbal remedies	<ul style="list-style-type: none"> Check for possible drug interactions with new medication or medication that may increase bleeding risk or merit dose reduction; consider choosing an agent that is less likely to interact with DOAC
Managing bleeding complications	
Haemorrhage	Stop DOAC and refer patient immediately to A&E if serious bleeding occurs e.g., GI-bleeding, epistaxis lasting more than 1 hour
Serious Trauma (especially to the head)	Withhold DOAC and refer to A&E
Unexplained acute drop in Hb or BP	Withhold DOAC and refer for urgent investigations
Excessive bruising	Seek urgent specialist advice

11. Cockcroft & Gault (C&G) formula^{3,13–16,33–36}

- The MHRA produced a drug safety update which states that **creatinine clearance must be calculated using the Cockcroft-Gault formula** to determine dosage adjustments for DOACs to reduce the risk of bleed by ensuring appropriate dosing.
- eGFR and calculated creatinine clearance (CrCl) are NOT interchangeable – **do not use eGFR for DOAC dosing.**
- Creatinine clearance calculators built into prescribing software (e.g., EMIS) should not be used as there is ambiguity about which weight is used
- Use actual body weight to calculate CrCl (Cockcroft-Gault) for patients who are either within a healthy weight range or are underweight
- If obese (i.e., >20% over ideal body weight), then online electronic calculators (such as MDcalc) can take height into consideration when estimating CrCl
 - There are also online calculators to determine whether the patient's actual weight is >20% of their ideal body weight (e.g., [MDCalc](#))

Example of electronic CrCl (C&G) calculator

<https://www.mdcalc.com/calc/43/creatinine-clearance-cockcroft-gault-equation>

Manual calculation of CrCl (mL/min) using C&G formula

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{constant}}{\text{serum creatinine } (\mu\text{mol/L})}$$

- Constant = 1.23 (male) or 1.04 (female)
- Weight (kg) = **current weight** or **adjusted body weight (ABW)** if obese*

*Obese defined as >20% over ideal bodyweight (IBW)

- **Adjusted body weight (ABW) =**
Ideal body weight + 0.4 (current body weight - ideal body weight)

12. Management of DOAC around elective MINOR procedures

- The management of anticoagulation around elective procedures is a balance of thrombosis (venous/arterial) vs the risks of bleeding complications. DOACs are simpler to manage peri-procedurally than warfarin, and LMWH bridging is not required
- Patients at high risk of thrombosis (e.g., VTE/CVA/TIA within the previous 3 months, antiphospholipid syndrome, or anti-thrombin deficiency, CHASD₂VASc₂ ≥7) should be discussed with the patient's haematologist**

Suggested management for **MINOR PROCEDURES* in patients with low thrombotic risk** (*procedures considered to cause infrequent bleeding with low clinical impact and where adequate local haemostasis is possible).

Examples include:

- Minor dental interventions:** dental extractions (1-3 teeth), implant positioning, paradental surgery, subgingival scaling/cleaning
- Superficial surgery:** abscess incision, small dermatologic excisions, skin biopsies
- Ophthalmology:** cataract or glaucoma intervention with minimal bleeding risk
- If estimated CrCl <30mL/min:** discuss with secondary care anticoagulation clinic (*NB: dabigatran contraindicated*); a longer interval between last dose of DOAC and procedure may be required.
- If unsure as to the management of a particular patient:** discuss with secondary care anticoagulation clinic
- Aim for morning procedure at the beginning of the week (so that any bleeding complications can be dealt with within surgery hours)
- Opt for simple analgesia post procedure (e.g. paracetamol) and avoid NSAIDs

Suggested DOAC management is outlined in the table below (adapted from ref 9)

DOAC	2 days before procedure	1 day before procedure	Day of procedure	Day 1 post*
Apixaban BD	Take as normal	Take morning dose; Take last dose no later than 6pm	No DOAC	Restart AM
Dabigatran BD (≥50ml/min)	Take as normal	Take morning dose; Omit evening dose	No DOAC	Restart AM
Dabigatran BD (30-50ml/min)	Take as normal	Omit morning and evening doses	No DOAC	Restart AM
Edoxaban Rivaroxaban (OD)	Take as normal	If usually takes AM, take dose no later than 8am	No DOAC	Restart AM
	Take as normal	If usually takes PM, take dose no later than 6pm and schedule procedure approximately 18 h after the last dose	No DOAC	Restart evening

Post-procedure

- Optimise local haemostasis
- *Delay restarting DOAC if there are any concerns re bleeding; discuss with local haematologist as appropriate
- Peak drug levels (i.e., therapeutic anticoagulation) are reached 2-4 hours post oral dose
- Rivaroxaban must be taken with food to maximise oral absorption

For patients undergoing more complex procedures with higher bleeding risks e.g., in-patient procedures (including day surgery) or major surgery: management plans should be arranged by the pre-assessment clinic or the responsible speciality team of the trust where the procedure will be undertaken. These patients will need to be assessed in terms of thrombosis and bleeding risk and DOAC withheld as per local secondary care guidelines. Post-procedure plans should be communicated to the GP in the discharge paperwork.

13. Referrals and contact information

Complex cases must be referred to an NCL specialist using either the [NCL anticoagulation referral form](#) or your standard referral pathway.

Please ensure every referral includes:

- Indication for anticoagulation
- Clinical context of the query
- If for AF, the current CHA₂DS₂-VASc score
- Bleeding risk using the HASBLED or ORBIT tool
- Up to date relevant bloods and trends
- Up to date weight
- List of medications
- Any specific concerns

NCL anticoagulation clinics

A formal referral mechanism is in place via eRS across NCL. All information on anticoagulation clinics can be found on the NCL GP website: https://gps.northcentrallondon.icb.nhs.uk/topic/anticoagulation	
Royal Free London	rf.acc@nhs.net
Barnet and Chase Farm Hospital	bcf-tr.dawnac@nhs.net
University College London Hospitals	uclh.referrals.anticoag@nhs.net
Whittington Health	whh-tr.anticoagulation@nhs.net
North Middlesex University Hospital	northmid.anticoag1@nhs.net

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