Frequently asked questions (FAQs) concerning Direct Acting Anticoagulants (DOACs) for primary care practitioners in South East London

This guidance has been written by anticoagulation specialists in South London in answer to common questions received by anticoagulation teams and medicines optimisation teams in South East London from healthcare practitioners (HCPs) concerning patients taking DOACs.

The aim of this guidance is to provide information to assist HCPs with queries concerning DOACs and advice concerning when a referral and/or further investigation is appropriate for their patient.

The guidance has been reviewed by the South London Cardiovascular Medicines Working Group and approved by the South East London Integrated Medicines Optimisation Committee.

Index for FAQs:

Approval Date: September 2020 **Review Date:** September 2022 (or sooner if indicated)

<table>
<tr><th>Question:</th><th>Answer:</th></tr>
<tr><td>1. How should patients at higher risk of bleeding be monitored?</td><td>There is no standard approach. It depends on the bleeding risk and clinical circumstances. Patients should be counselled to monitor for signs of bleeding and to report to their general practitioner (GP) or emergency department (ED) as appropriate.

This advice is the same as for warfarin patients although it should be noted that the risk of major bleeding, particularly intracranial haemorrhage, is significantly reduced with DOACs.</td></tr>
<tr><td>2. What to do if haemoglobin (Hb) drops?</td><td>If Hb <100g/L or change from baseline >20g/L, investigate for cause and consider referral to/review by a specialist based on initial investigations.
Referral will depend on the suspected underlying cause: –
1) If GI bleeding/cancer will need referral to gastroenterology/colorectal
2) If menorrhagia is not controlled with measures offered, consider a gynaecology referral +/-haematology advice re. choice of anticoagulant.
3) For haematuria – urology referral +/- haematology advice if ongoing bleeding is an issue
The relevant specialist may not always be a haematologist.
Depending on the clinical context and degree of Hb drop, consider stopping anticoagulation and investigate for the cause of Hb drop or low Hb as necessary, and in line with NICE recommendations for cancer investigations.
Stopping anticoagulation may be temporary while investigations occur.</td></tr>
<tr><td>3. What to do if renal function (creatinine clearance) is impaired?</td><td>Calculate creatinine clearance (CrCl) as per SEL guidance: link

Adjust DOAC dose as per summary of product characteristics (SPC) for the DOAC agent (via www.medicines.org.uk): (see DOAC initiation/monitoring template):

<table>
<tr><th>SPC hyperlinks:</th><th>Edoxaban</th><th>Rivaroxaban</th><th>Apixaban</th><th>Dabigatran</th></tr>
<tr><td>Standard dose</td><td>60mg OD</td><td>20mg OD (with food)</td><td>5mg BD</td><td>150mg BD</td></tr>
<tr><td>Reduced dose</td><td>30mg OD</td><td>15mg OD (with food)</td><td>2.5mg BD</td><td>110mg BD</td></tr>
<tr><td>Criteria for reduced dose</td><td>≥ 1 of
· weight ≤ 60kg
· CrCl 15-50ml/min
· On ciclosporin, dronedarone, erythromycin ketoconazole</td><td>CrCl 15 to 49ml/min</td><td>≥ 2 of;
· Age ≥ 80yrs
· weight ≤ 60kg
· Cr ≥ 133µmol/L
OR
CrCl 15-29ml/min</td><td>· Age ≥ 80 yrs
· On verapamil
· Consider for
o Reflux/gastritis
o Age 75-80 yrs
o CrCl 30-50ml/min
o “Bleed risk”</td></tr>
<tr><td>Contra-indicated</td><td>CrCl <15ml/min (caution CrCl >95ml/min)</td><td>CrCl <15ml/min</td><td>CrCl <15ml/min</td><td>CrCl <30ml/min</td></tr>
</table>

Continue to monitor the patient with the frequency dictated by the SEL renal monitoring (CrCl) guidance, including at least 6 monthly monitoring for elderly DOAC patients aged over 75 years and frail patients</td></tr>
</table>

	If CrCl is <15ml/min (<30ml/min for dabigatran) DOACs are contra-indicated, stop DOAC and refer back to anticoagulation for urgent switch to warfarin. Dialysis patients –discuss with the renal team regarding suitability for anticoagulation. The risk/benefit profile of anticoagulation in AF for dialysis patients is not clear.
4. What to do if platelets drop?	Any platelet count below 100 should be monitored closely and investigated further: If platelet count is 50-75: monitor closely (at least monthly) and advise patient to report any bleeding. Refer to local haematology clinic for further investigation as appropriate. If platelets <50 – advise patient to stop taking anticoagulant and seek advice from local anticoagulation/haematology team.
5. What to do if liver function changes?	If liver transaminases: AST or ALT >2 x upper limit of normal (ULN) or bilirubin >1.5 x ULN, or if liver disease is associated with clinically relevant bleeding risk e.g. presence of varices – discuss with local anticoagulation clinic.
6. How do you dose peri-surgery?	See table below

Drug	**When to stop DOAC therapy pre-operatively**		
Dabigatran	Renal function (CrCl ml/min)	High risk of bleeding or major surgery	Standard risk of bleeding
	≥80	48 hours	24 hours
	≥50-<80	48-72 hours	24-48 hours
	≥30-<50	96 hours	48-72 hours
Rivaroxaban	Renal function (CrCl ml/min)	High risk of bleeding or major surgery	Standard risk of bleeding
	≥30	48 hours	24 hours
	<30	72 hours	48 hours
Apixaban	Renal function (CrCl ml/min)	High risk of bleeding or major surgery	Standard risk of bleeding
	≥30	48 hours	24 hours
	<30	72 hours	48 hours
Edoxaban	Renal function (CrCl ml/min)	High risk of bleeding or major surgery	Standard risk of bleeding

	≥30	48 hours	24 hours
	<30	72 hours	48 hours

Advice will be given to primary care from the pre-assessment clinic- seek further advice from the surgical or haematology team, or initiating clinician/dentist if this is unclear.

	When to re-start DOAC therapy post-operatively		
All DOACs	Renal function (CrCl ml/min)	High risk of bleeding or major surgery	Standard risk of bleeding
	All	Use prophylactic parenteral anticoagulation (eg. dalteparin 5000 units OD if <100kg) from 6-12 hrs. post op if haemostasis is achieved, then resume DOAC at 48 hours post op.	Resume DOAC 6-12 hours post op as long as haemostasis has been achieved
		Administration time can be moved by an hour a day to allow resumption of original dosing routine.	

The DOAC will be restarted by the hospital surgical team or anticoagulation clinic post operatively and/or bridged with LMWH (eg dalteparin or enoxaparin) as necessary.

See: https://www.sps.nhs.uk/wp-content/uploads/2016/09/swmitrtdc-OAC-comparison-jan16-final-Version-2.1.pdf for further information concerning type of surgery and bleeding risk.

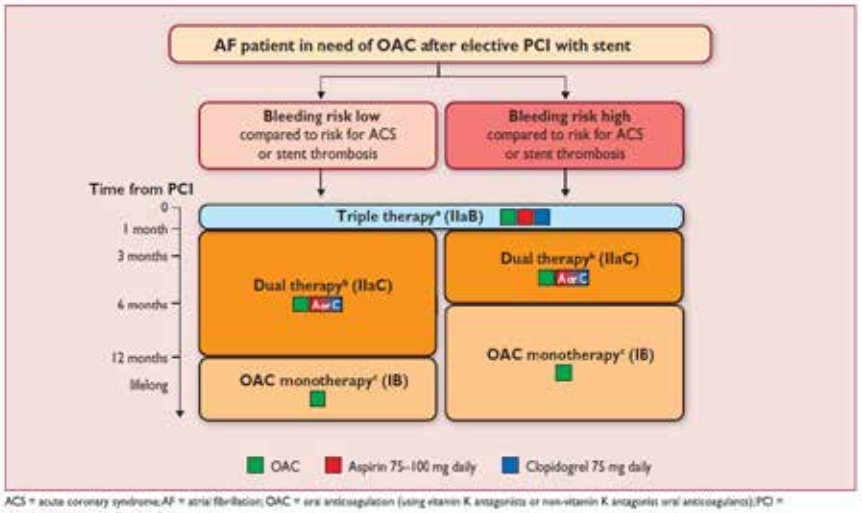
7. How should frail patients at high falls risk be managed?

For these patients no dose reduction is required and anticoagulation should not be withheld if the CHADVASc score is high. A study by *Man-Son-Hing et al Arch Intern Med. 1999;159:677-685* showed that a patient would have to fall >295 times/year for the risks associated with warfarin therapy to outweigh the benefit. This data can be extrapolated to the DOAC population.

If you have concerns about a cerebral bleed risk or would like further advice please refer to the local falls clinic or haematologist.

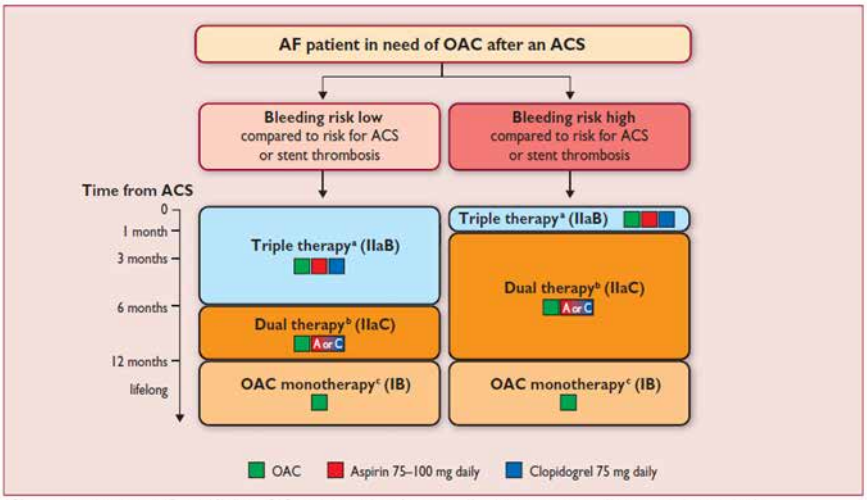
Renal function, liver function and haemoglobin for frail patients should be monitored every 6 months regardless of age.

8. When should antiplatelets be reviewed in combination with oral anticoagulation (OAC)?	When starting a patient on a DOAC, if they are already on an antiplatelet, the time of the last cardiovascular event should be established. If it was more than one year ago then the antiplatelet can usually be stopped. However, if these patients are under the care of a cardiologist, stroke or vascular specialist, they should be consulted as balancing the clinical need for anticoagulant and antiplatelets is often a complex decision based on more than one factor (*refer to SEL antiplatelet guidance- update under consultation*)



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 13 Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation.



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 12 Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

The tables above are a guide as to how triple therapy should be managed for cardiology indications and the durations you may expect to see, reference:

https://academic.oup.com/eurheartj/article/39/16/1330/4942493

There is no standardised approach for patients with cerebrovascular or vascular indications for antiplatelets.

9. Can patients being investigated for cancer be treated with DOACs?	For a new presentation of an unprovoked venous thromboembolism (VTE) to secondary care, patients will be started on low molecular weight heparin (LMWH) over a DOAC whilst they undergoing urgent (2 week wait) investigations. Only if the results are negative, or under specialist haematology guidance, would the patient be switched to a DOAC. If a patient is undergoing investigations for cancer when already established on a DOAC, the DOAC should be continued unless the patient has presented with bleeding (the risk of bleeding verses the risk of stroke should be weighed up in this instance). The oncologist or haematologist investigating the cancer should be reviewing the choice of anticoagulant and switching to LMWH if appropriate. If you do not think that the anticoagulant has been considered, please contact them for advice. See 12. **Can DOACs be prescribed in patients with malignancy?** for more information on confirmed cancer diagnosis.
10. What if my patient has haematuria?	Patients taking DOACs are managed by the same pathway as when haematuria is investigated or managed in general practice. Whilst it is a listed side effect of all DOACs, the cause of the haematuria should still be fully investigated. It would be prudent to also check full blood count (FBC), urea and electrolytes (U+Es) and renal profile (CrCl). The DOAC should be continued whilst awaiting investigations where possible, after assessing the risk of stroke against the risk of bleeding (involving the patient in this discussion). Where a patient has significant haematuria that is ongoing, or a Hb drop where this is the likely source, withholding the DOAC (temporarily while this is investigated) may be appropriate. Consider the patient's HASBLED score (https://www.mdcalc.com/has-bled-score-major-bleeding-risk) and modifiable risk factors for bleeding, as these should be optimised/minimised when prescribing DOACs.
11. Nosebleed and other minor / nuisance bleeding?	In general, patients should be counselled on DOAC initiation and at every review that should nuisance and minor bleeding occur, to continue the DOAC unless otherwise advised by a healthcare professional. It would be prudent to check FBC, U+E and Renal Profile on presentation. **Nose Bleeds:** Patients should be advised to practice first aid (as outlined here:- https://cks.nice.org.uk/epistaxis-nosebleeds) should a nosebleed occur. If the nosebleed does not stop after 10-15 minutes of nasal pressure, they should attend A+E. It is likely that the patient will be advised to miss one dose of the DOAC. If first aid measures result in the cessation of bleeding within 10-15 minutes the patient does not need to attend A+E or miss any doses of DOAC. In all instances, the patient should be advised to avoid activities that increase the risk of re-bleeding for 24 hours e.g. blowing the nose or heavy lifting. If nose bleeds are recurrent, ask the patient to record how often these are occurring, for how long, and if they have missed any doses of the DOAC. Assess the cause of the nose bleeds (as outlined here: https://cks.nice.org.uk/epistaxis-nosebleeds#!scenarioRecommendation:1) and, if needed, prescribe topical treatment with an antiseptic preparation.

	In some circumstances an ENT referral may be required. A patient information leaflet on epistaxis can be found here: https://www.entuk.org/sites/default/files/files/ENT/About%20Epistaxis%206pp%20DL%20(09021)_7_16.pdf **Bleeding Gums:** Bleeding gums usually occur when brushing teeth or flossing. Patients should be advised not to miss any doses of the DOAC and that bleeding gums are a harmless side effect. The most likely cause is plaque-induced gingival inflammation and hence patients should be advised to follow good oral hygiene and attend for regular check-ups at the dentist. Should the bleeding gums be excessive or prolonged, refer the patient to the dentist / periodontist for a through dental examination.
12. Can DOACs be prescribed in patients with malignancy?	AF treatment: Little evidence for this cohort. Ideally keep on current anticoagulant (DOAC or warfarin) Consider drug-drug interactions (with chemotherapy) and creatinine clearance (CrCl). Consider bleeding risk and thrombosis risk (cancer not a factor in either HASBLED or CHA_2DS_2VASc) and patient wishes if de-prescribing anticoagulation. VTE treatment: Evidence to show can use DOACs in active cancer patients. Low-molecular weight heparins (LMWHs) are preferred for patients with gastrointestinal malignancies or high risk of bleeding. *Hokusai VTE Cancer study 2018* · Edoxaban vs. dalteparin · Edoxaban was non-inferior to dalteparin for the combined outcome of recurrent thrombosis and major bleeding. *SELECT-D trial 2018* · Rivaroxaban vs. dalteparin in patients with cancer · Rivaroxaban was associated with a lower risk of recurrent VTE
13. Is there an antidote for DOACs?	Outcomes of major bleeds with DOACs are no worse than those with warfarin even in the absence of clinically available antidotes. There is a 50% reduction of intracerebral haemorrhage (ICH) and fatal bleeds with DOACs compared with warfarin, although the absolute reduction is limited to 2 intracranial bleeds and 1 fatal bleed per 1000 patients per year. Gastrointestinal haemorrhage was more frequent in patients taking DOACs than warfarin. DOACs have a short half-life so withholding the medication and supportive care should be utilised in all circumstances of major bleeding. Haematology and Emergency departments in hospital can advise on use of activated charcoal, tranexamic acid and prothrombin complex concentrates. The only antidote currently available is Idarucizumab – for the rapid reversal of dabigatran. It may be necessary for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

14. What references are available for dosing queries?	For DOACs the dose reduction criteria varies between agents and indications. For the most up-to-date dosing please refer to the Summary of Product Characteristics (SPC) for each DOAC at: https://www.medicines.org.uk/emc/ Guy's and St Thomas' (GSTT) has a free "Thrombosis Guidelines" app which is available on both android and iphone. This app includes GSTT guidance on treatment and prevention of VTE, DOAC dosing, management of over-anticoagulation and warfarin.
15. How do I counsel patients? Who can I refer to?	There is a counselling checklist included as part of the DOAC initiation and monitoring guidance There are patient materials available to support patient education, including printed leaflets and websites: AF Association https://www.heartrhythmalliance.org/afa/uk/ Anticoagulation UK https://www.anticoagulationuk.org/ British Heart Foundation https://www.bhf.org.uk/ For patients with a history of venous thromboembolism: Thrombosis UK https://thrombosisuk.org/ Many of the acute hospital trusts and pharmaceutical companies have their own patient information leaflets (PILs) which should be provided to patients. Guy's and St Thomas' (GSTT) has an information app for patients, providing information videos about AF, amongst other conditions: https://www.guysandstthomas.nhs.uk/our-services/cardiovascular/medtap.aspx Community pharmacists and practice-based pharmacists can also help support DOAC adherence and understanding. **For anticoagulation cards** (OAT alert): Supplier for GP Practices now Primary care Support England not Xerox via nhs.forms.co.uk: Email: pcse.supplies-leeds@nhs.net OR PCSE.DataManager@nhs.net OR PCSE.AdHoc-MR@nhs.net
16. For housebound patients, how will they be weighed before initiation and for follow ups?	Patients will be weighed at initiation, during an inpatient stay or in outpatient clinics. Telephone initiations are only done at the clinician's discretion and the current weight will be confirmed with the patient or in the medical records. It is recommended that patients are weighed at least annually, as part of their annual anticoagulation review in primary care, and to enable an accurate calculation of creatinine clearance (CrCl).
17. How do I switch to edoxaban or rivaroxaban from another DOAC? From warfarin? (*SEL preferred DOAC agents*)	Continued anticoagulant therapy is vitally important in patients with NVAF. According to the summary of product characteristics (SPC: www.medicines.org.uk), discontinue dabigatran or apixaban and start edoxaban or rivaroxaban at the time of the next dose of the oral anticoagulant (e.g. normally the following morning). It would be good practice to review the patient at 6 to 8 weeks after the switch to confirm that they are tolerating the change in DOAC. Patients should be advised to use up the supply of original DOAC before starting the newly prescribed edoxaban or rivaroxaban in order to negate any wastage (medication costs, dispensing costs/pharmacist time etc).

	In all cases exercise clinical judgement and ensure that, if the patient is under a specialist, that they have been consulted (eg advice and guidance), and previous correspondence has been reviewed, before switching (unless switching due to drug intolerance- report all significant suspected reactions to DOACs to the Yellow Card Scheme (www.mhra.gov.uk/yellowcard). Speak to anticoagulation (AC) specialist pharmacists for advice if needed. See **warfarin to DOAC switching** guidance from COVID-19 pandemic, appendix 1: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf Seek advice and guidance from your local anticoagulation clinic for patients switching from warfarin and for their follow up/monitoring requirements.
18. How do I find out what medicines interact with DOACs? How do I manage them?	Please refer to the British National Formulary (BNF) and Summary of Product Characteristics (SPC) for the DOAC agent for further details: BNF: https://bnf.nice.org.uk/interaction SPC: www.medicines.org.uk For HIV medications see: https://www.hiv-druginteractions.org/ Common interactions to consider are with antiepileptic agents, HIV antiretrovirals, hepatitis antivirals, antifungals and chemotherapy agents. Some DOACs require a dose adjustment, some require more frequent monitoring and, in some cases, should not be prescribed in combination with interacting medicines. Please consult a pharmacist for advice.
19. What happens if my patient develops a skin rash on a DOAC?	Maculopapular rashes are drug-induced in approximately 50 to 70% of adult patients, and should be a suspected cause if a skin rash begins within 4 to 12 days of starting a new medicine, although some rashes may occur later. If the timing of onset of the skin rash fitted with when the DOAC started, and there is no other cause, then try switching to an alternative DOAC to see if the rash improves. If the rash is very mild then the patient may be happy to continue for short while to see if the rash improves on the same DOAC. Please note: Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions. This rare reaction may also be possible with other DOAC agents (as with other medications) but have not been reported in literature.
20. Contact details (email) for local anticoagulation services in SEL	· For UHL: **LH.Anticoagulation@nhs.net** · For QEH: **LG.QEAnticoagulant@nhs.net** · For PRUH: **kch-tr.br-anticoag@nhs.net** · For KCH: **kch-tr.dh-anticoag@nhs.net** · For GSTT: **gst-tr.anticoag@nhs.net** · Bexley, for community service: anticoag.bellegrove@nhs.net · Bromley, for Boots community service: muhammad.patel@boots.co.uk