Guideline for managing bleeding in patients treated with Non Vitamin K Antagonist Oral Anticoagulant drugs (NOACs)

Introduction

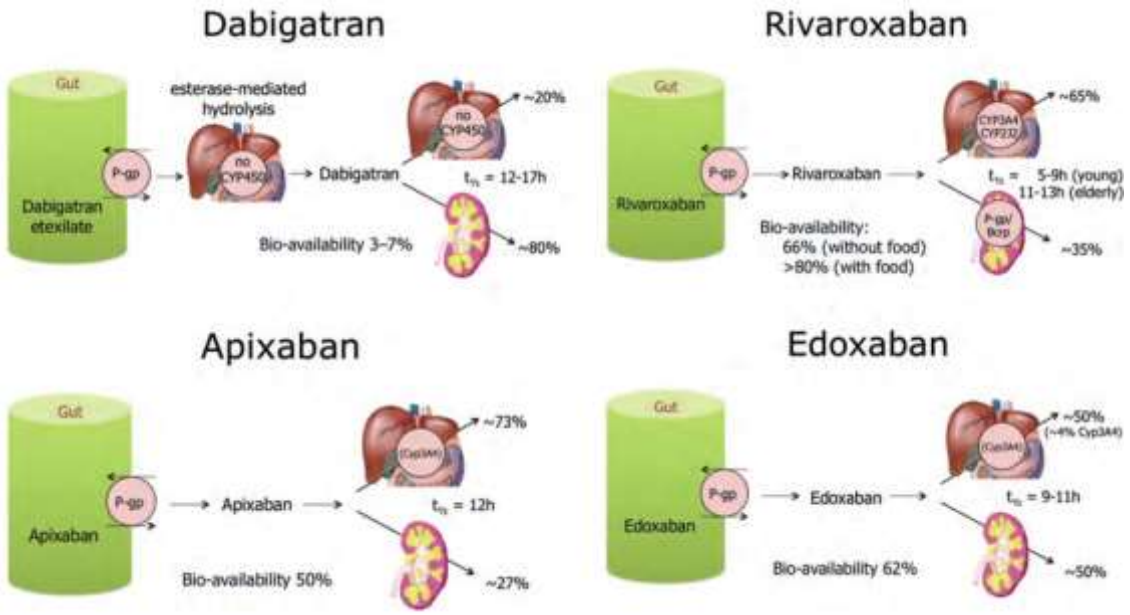
Two new classes of anticoagulant drugs have been developed: they are both oral formulations that do not require regular monitoring.

- Direct thrombin inhibitors: Dabigatran
- Direct Xa inhibitors: Rivaroxaban, Apixaban and Edoxaban

NOACs (New/Novel/Non VKA Oral Anticoagulants) also referred to as Oral Direct Inhibitors (ODIs) and Direct Oral Anticoagulants (DOACs) are licensed and NICE approved for a number of indications including thromboprophylaxis after elective hip and knee replacement, prevention of stroke in non-valvular Atrial Fibrillation and treatment of Deep Vein Thrombosis and Pulmonary Embolism.

When deciding whether to use warfarin or a NOAC, advantages and disadvantages should be considered.

Figure 1: Absorption and metabolism of NOACs (EHRA practical guide Europace (2013) 15, 625–651)



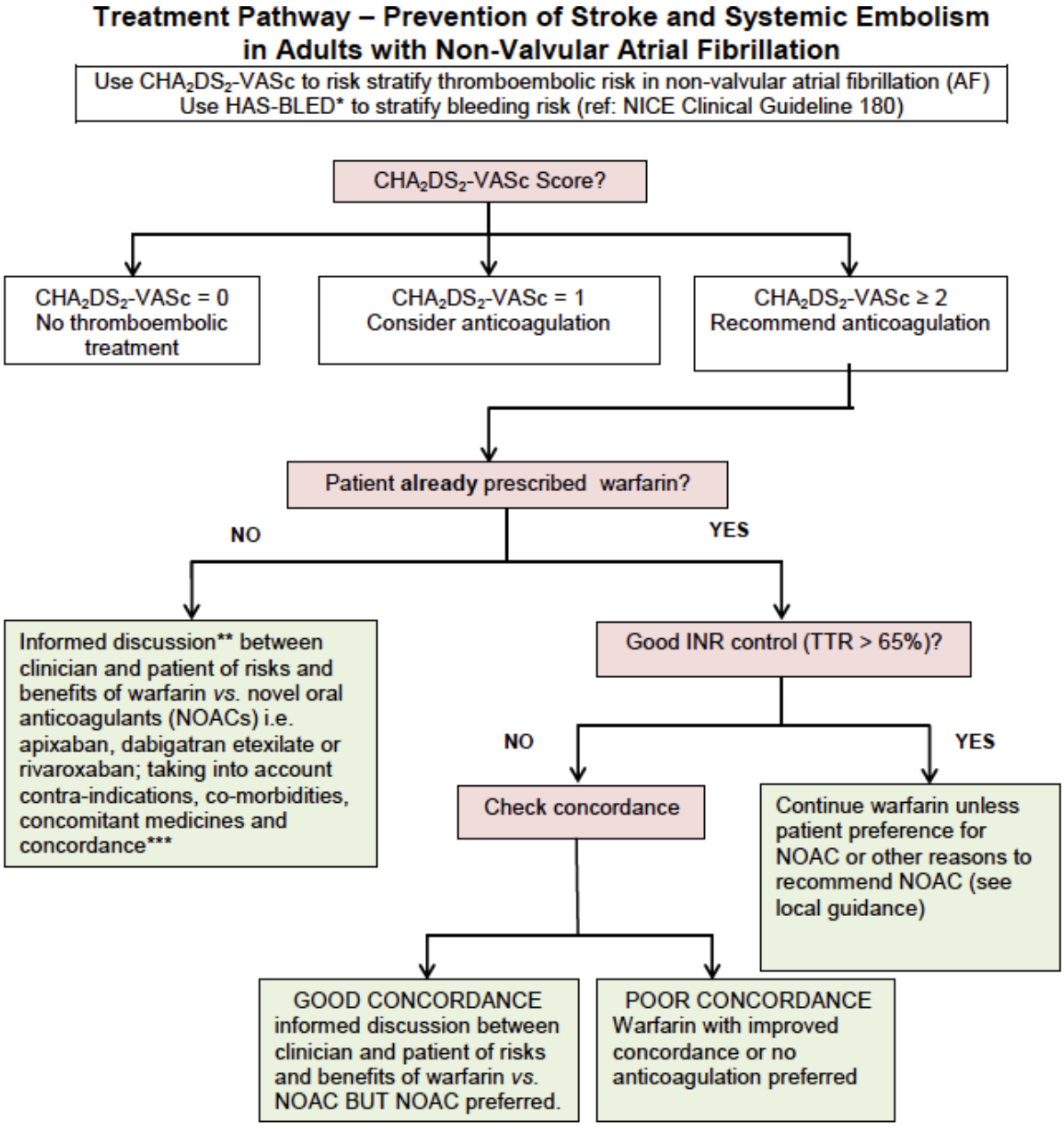
Management of bleeding in patients on a NOAC

- Manage bleeding as per usual *and in addition:*
- Try and establish the timing of the last dose and renal function to calculate the clearance of the drug (see figure 1)
- Discuss with on call haematologist
- Basic laboratory tests (PT, APTT) may give a 'feel' for the presence of a NOAC (Dabigatran and Rivaroxaban but not Apixaban).
- Consider Tranexamic acid 1g as intravenous bolus
- Consider Prothrombin Complex Concentrate (eg. Beriplex 25-30units/kg) for more refractory bleeding
- Dialysis may be considered for patients on Dabigatran (not Rivaroxaban or Apixaban)
- Activated charcoal can be considered if drug taken within 2-3 hours (consider for up to 6 hours after Apixaban ingestion)

Switching

- When switching from a LMWH, prescribe the NOAC to be administered when the next dose was due.
- When switching from IV unfractionated heparin to a NOAC, stop the infusion at the same time as the first dose is given
- When switching from warfarin to an NOAC, do this when the INR is <2.0 (or <3.0 for Rivaroxaban for AF).
- When switching from a NOAC to warfarin, ensure they overlap until the INR is well over 2.0 (measure the INR at trough NOAC concentrations).
- It is important you refer to the BNF and/or drug SPC when you co-prescribe other medicines.
- If a cardiology procedure is required eg. cardioversion/ablation, please discuss with cardiologist about which anticoagulant is preferred

Appendix 1:



*HAS-BLED ≥3, high bleeding risk, consider reversible causes for bleeding e.g. aspirin/NSAID use, uncontrolled hypertension, labile INR, and consider risk of bleeding *vs.* risk of stroke – usually the balance remains in favour of stroke prevention.
**Please notify anticoagulant team of all new patients when there is an intention to intiate a NOAC. A PICS referral can be made for follow up after discharge
*** Caution with NOAC in patients with high bleeding risk including: very elderly e.g. age >80, previous bleeding event, HAS-BLED ≥3, low body weight < 60kg, renal impairment (Manufacturer advises to avoid apixaban if eGFR< 15ml/min; dabigatran contraindicated if eGFR<30ml/min; rivaroxaban contraindicated if eGFR<15ml/min, caution if eGFR 15-30ml/min).
INR = International Normalised Ratio; TTR = Time to Therapeutic Range; eGFR: estimated Glomerular Filtration Rate

Appendix 2: Summary of NOAC characteristics

Dabigatran etexilate (Pradaxa®) is a direct thrombin inhibitor, licensed and NICE approved for:

1. Thromboprophylaxis following Total Hip Replacement (THR) and Total Knee Replacement (TKR) in adults. << link http://www.nice.org.uk/guidance/TA157
2. Prevention of stroke and systemic embolism in non valvular Atrial Fibrillation (AF) and one or more of the following risk factors: www.nice.org.uk/guidance/TA249

- History of stroke, TIA or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure NYHA Class II or above
- Age ≥75 years
- Age ≥65-years with one of diabetes mellitus, coronary artery disease or hypertension

Indication		Dose	Dose in moderate renal impairment*	Duration
VTE prophylaxis	Knee replacement	220 mg ONCE daily within 1-4 hours of surgery	150 mg ONCE daily within 1-4 hours of surgery	10 days
	Hip replacement	220 mg ONCE daily within 1-4 hours of surgery	150 mg ONCE daily within 1-4 hours of surgery	28-35 days
Prevention of stroke and systemic embolism	In NVAF with one or more risk factors (as above)	150 mg TWICE a day	110 mg TWICE a day	Long-term

*Moderate renal impairment 30-49 ml/min

Notes:

- A forgotten dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours onwards prior to the next scheduled dose, the missed dose should be omitted. No double dose should be taken to make up for a missed dose.
- Dose adjustments for renal function are based on the Creatinine Clearance (CrCl) in the licence for dabigatran. Therefore calculate the renal function using the CrCl and not the eGFR.
- Avoid in patients with severe renal impairment (GFR<30) or hepatic impairment
- No dose adjustment is required for mild renal impairment (CrCl 50-80 ml/min)
- The dose reduction for moderate renal impairment above also needs to be considered for patients with a high risk of bleeding:
    - Aged ≥75 years
    - Low body weight < 50 kg
    - Pharmacodynamic interactions that increase the risk of bleeding (e.g. concomitant NSAIDs, clopidogrel, SSRIs)

    - Patients who receive concomitant verapamil, amiodarone, quinidine (i.e. mild to moderate P-glycoprotein (P-gp) inhibitors
- A common side-effect of dabigatran is dyspepsia, which is reduced if taken with food (a PPI can also be used)
- Anticoagulants and antiplatelets - concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold.
- NSAIDs - due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.
- Concomitant administration of strong P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole and clarithromycin) is expected to result in increased dabigatran plasma concentrations. If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors.
- Close monitoring should be exercised when dabigatran etexilate is combined with clarithromycin and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.
- Itraconazole, tacrolimus and cyclosporine are contra-indicated.
- Inadequate clinical data is available regarding the co-administration of dabigatran and dronedarone and their co-administration is not recommended.
- Concomitant administration of a P-gp inducer (such as rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran concentrations and should be avoided.
- Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer) have not been studied and are therefore not recommended for concomitant treatment with dabigatran.
- SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups