GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Caerdydd a'r Fro | Cardiff and Vale University Health Board

Prevention of stroke and systemic embolism in atrial fibrillation – NICE CG 180

Recommendation of the Medicines Management Group of Cardiff and Vale University Health Board June 2015

- For all patients with non-valvular atrial fibrillation (AF) where anticoagulation is indicated, warfarin is a suitable 1st line oral anticoagulant option.

- A Direct Oral Anticoagulant (DOAC) may be considered as an option for patients:
  - with intolerable side-effects or allergy to warfarin **OR**
  - who fail to achieve good* INR control despite evidence of good compliance† **OR**
  - who are unable to take warfarin **OR**
  - where the benefit of DOAC outweighs risk of warfarin for the individual **AND**
  - who meet the licensed therapeutic indication. DOAC not indicated for anticoagulation of patients with artificial heart valves. Warfarin is the anticoagulant of choice.

A DOAC may be initiated in line with the above, following documented risk-assessment and informed patient consent.

* Good INR control means absence of unexplained recurrent INR variations < 1.5 / > 5, or time in therapeutic range (TTR) >60% (- where available systems support calculation of TTR).

- † Many of the causes of poor compliance with warfarin may also result in non-compliance with DOACS. Non-compliance is therefore not a reason to switch anti-coagulant treatments. Poor compliance with DOACS is likely to be associated with increased risk of bleeding or thrombosis. Noncompliance should trigger review of the appropriateness of continuing with treatment.
- Unlike warfarin, treatment with DOACS does not necessitate routine coagulation (INR) monitoring. However routine monitoring of the patients renal function and FBC is recommended.
- Significant drug-drug interactions may occur with DOACS, so care must be exercised when initiating a new medication or stopping and existing medication
- There is now a licensed antidote for Dabigatran (Idarucizumab) available in UHW. Practitioners should refer to current guidelines in selecting the best anti-coagulant for the patient.

Further details on choice of oral anti-coagulant; contraindications; pre-treatment testing and ongoing monitoring; advice on switching between oral anti-coagulants and known interactions can be found in this document:

SUMMARY OF PRODUCT CHARACTERISTICS (SPC) MUST BE REFERRED TO BEFORE PRESCRIBING OR RECOMMENDING TREATMENT WITH DOAC

Author/contact person & email: Tristan.groves@wales.nhs.uk	Date written: June 2015 –updated March 2019
Clinical Board: Cardiff & Vale	Date of cMMG approval: 20th Aug 2015
Version: 1.4	Review date: March 2020
CBP approval : Cardiff & Vale MMG Aug 2015	Format/posting approval: (DF/GW & date

Atrial fibrillation: stroke risk assessment and antithrombotic treatment recommendation

Initiating prescriber responsibilities include:

- Patient's risk of stroke must be assessed and their **CHA_2DS_2VASc** score documented. Their bleeding risk must also be assessed and documented, using the **HAS-BLED** tool. Patients must be educated with regard to risks and compliance and informed consent to treatment obtained and documented, using a patient decision tool as appropriate

- The following baseline tests must be undertaken and the results reviewed:

    - Blood pressure
    - Body weight
    - Full blood count
    - Clotting screen (PT and APTT)
    - Urea & electrolytes
    - Creatinine clearance (Cockcroft Gault)
    - Liver function

- Ensuring relevant documentation is available to patient's GP (if GP not initiator)
- Providing the provision of printed patient information, plus a patient alert card (available within the medication packet or via the manufacturer's website, for use in emergency situations. Examples of patient alert/information cards are available on-line, e.g:

- Apixaban alert card https://www.medicines.org.uk/emc/rmm/112/Document

- Dabigatran alert card https://www.medicines.org.uk/emc/rmm/401/Document

- Edoxaban alert card https://www.medicines.org.uk/emc/rmm/227/Document

- Rivaroxaban alert card https://www.medicines.org.uk/emc/rmm/625/Document

- Completing the CAVUHB counselling documentation with the patient. Following point(s) to be highlighted to patient:
    - Signs or symptoms of bleeding and when to seek attention from a healthcare professional
    - Importance of treatment compliance
    - To carry the Alert Card with them at all times
    - The need to inform a healthcare professional that (s)he is taking DOAC if there is a need to have any surgery or invasive procedure, or if receiving unscheduled medical care

Initiating prescriber responsibilities include:

- Performing baseline evaluation of patient's creatinine clearance (CrCl) using the patient's **actual** weight and using a Cockroft & Gault calculator tool.

In patients where the creatinine clearance is borderline for dose reduction/contraindication it may be particularly important to consider other risk factors (see SPC) when choosing the most appropriate dose.
Regardless of whether this calculation is done manually or using the calculator the following should be considered:

- *Use 60 micromol/L if the creatinine concentration is < 60 micromol/L*
- *This equation may overestimate CrCl in elderly or malnourished patients*

Atrial fibrillation: stroke risk assessment and antithrombotic treatment recommendation

The patient's renal function should be used to guide appropriate dosing of the selected anticoagulant (see table below)

Calculated CrCl (ml/min)	≥80	79 – 50	49 - 30	29 - 15	<15
Apixaban	**5mg BD** Reduce dose to 2.5mg BD if ≥2 of the following: • Age ≥80 years • Weight ≤ 60kg • Serum creatinine > 1.5mg/dl (133µmol/L)			**2.5mg BD Used with Caution [1]**	**Not recommended**
Dabigatran	**150mg BD** Reduce dose to 110mg BD if: • Age ≥80 years • Patient on concomitant Verapamil Consider dose reduction if: • Age 75-80 Years • CrCl 30-50 ml/min • Patient at increased bleeding risk or history of gastritis,oesophagitis or GORD			**Not recommended**	
Edoxaban	**60mg OD** Reduce dose to 30mg OD if: • Weight ≤ 60kg • Patient on concomitant P-gp inhibitor		**30mg OD**	**30mg OD Use with caution [2]**	**Not recommended**
Rivaroxaban	**20mg OD**		**15mg OD**	**15mg OD Use with caution[3]**	**Not recommended**
Warfarin	**As per INR**				

	Dose reduction if additional risk factors		**Dose reduction based on CrCl**		**Dose reduction based on CrCl- used with caution see notes**		**Wafarin is an option for the prevention of strokes in patients with AF**

[1] **SPC for Apixaban** - For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily- **However limited clinical experience**

[2] **SPC for Edoxaban-** In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment or body weight <60kg, for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 30 mg once daily. **However limited clinical experience**

[3] **SPC for Rivaroxaban-** In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment , for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily. **However limited clinical experience**

Further information regarding dosing of DOACS in renal impairment:
https://www.sps.nhs.uk/articles/practice-guide-to-dosing-of-direct-acting-oral-anticoagulants-in-patients-with-renal-impairment/

Q: Can I prescribe a DOAC in patients at extremes of body weight?

- **ISTH guidelines recommend not using a DOAC in a patient > 120kg or BMI > 40**
- There is increasing experience in using DOACs in patients who weigh > 120kg
- The International guidelines state that if a DOAC is commenced in a patient with a BMI > 40 or weight > 120kg then measure a peak and trough drug level and if the level falls within the expected range, consensus opinion from the International guidelines is to continue the DOAC. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.13323

- ***Anticoagulation (warfarin or DOAC) in patients <50 kg should be used with caution***

Q: Can I prescribe a DOAC in Patients with liver impairment?

Medicine	Rivaroxaban[2]	Apixaban[3]	Dabigatran[4]	Edoxaban[5]
Use in hepatic impairment	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C	Prior to initiating apixaban, liver function testing should be performed. Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Caution in patients with mild or moderate hepatic impairment (Child Pugh A or B), but no dose adjustment is required. Caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN as these patients were excluded in clinical trials.	Contraindicated in hepatic impairment or liver disease expected to have any impact on survival Not recommended in mild-moderate hepatic impairment with liver enzymes >2 ULN.	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Use with caution in patients with mild-moderate hepatic impairment with liver enzymes >2 ULN or total bilirubin >1.5ULN.

ULN= Upper limit of normal

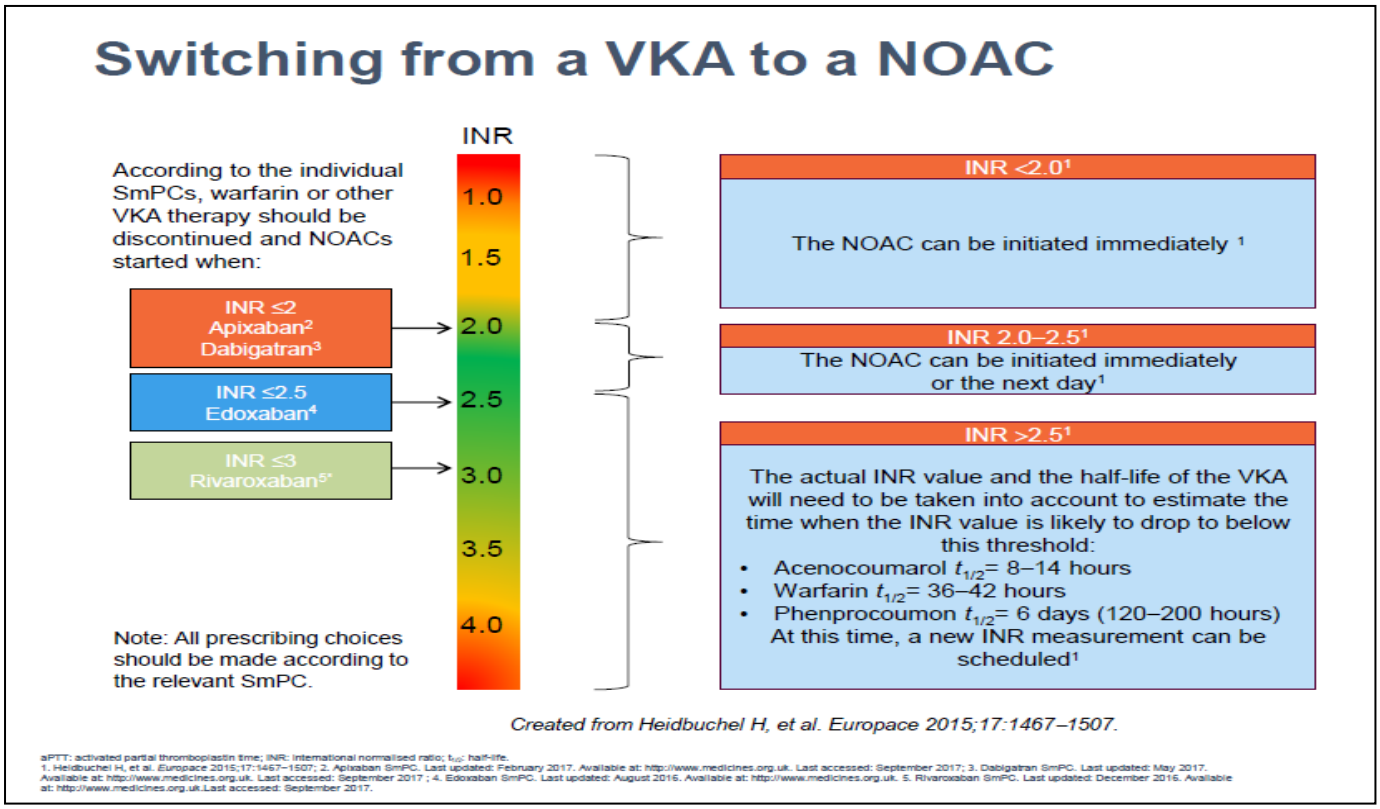
[2]SmPC- Rivaroxaban accessed 10/12/18 - https://www.medicines.org.uk/emc/product/2793/smpc [3] SmPC- Apixaban accessed 10/12/18 - https://www.medicines.org.uk/emc/product/2878/smpc
[4] SmPC- Dabigatran accessed 10/12/18 - https://www.medicines.org.uk/emc/product/4703/smpc [5] SmPC- Edoxaban accessed 10/12/18 - https://www.medicines.org.uk/emc/product/6905/smpc

GP responsibilities (if not initiating prescriber as above) include:
Ongoing prescribing for licensed indication, ensuring patient is monitored appropriately and dose adjusted as necessary. While on treatment, renal function should be assessed at least annually or whenever it is suspected that it could deteriorate. Patients with known renal impairment should have their renal function monitored as follows:

CrCl ml/min	Frequency of renal function monitoring required
≥60ml /min	Yearly - unless current condition may impact renal function
50-59 ml/min	Every 5 months - unless current condition may impact renal function
40-49 ml/min	Every 4 months - unless current condition may impact renal function
30-39 ml/min	Every 3months - unless current condition may impact renal function
20-29 ml/min	Minimum of every 2 months

As with all anticoagulants, DOAC should be used with caution in conditions with an increased risk of bleeding. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined. Treatment may need to be interrupted prior to surgery or invasive procedure – seek specialist advice.

Advice on switching from vitamin K antagonist



There is a licensed antidote for Dabigatran (available in pharmacy at UHW and UHL). Specific licensed antidotes for Apixaban and Rivaroxaban are not currently available. Apixaban half-life approx 12 hours. Rivaroxaban half life 5-9 hours, 11-13 hours in elderly. Dabigatran has a half-life of 12-17 hours (with normal renal function). Supportive therapy for severe haemorrhage may include transfusions of fresh frozen plasma, packed red blood cells and concentrated coagulation factor. Surgical/radiological intervention may be required.

In the event of bleeding advice must be sought from haematology coagulation team:

Mon – Fri 0900-1700 SpR Bleep 5886
Mon-Fri 1700-0900 and weekends – on call haematology SpR (via switchboard)

Consultant Haematologist (see clinical portal for on call rota): via switchboard.

Switchboard: 02920 747 747

Useful Contacts for further advice:

Anticoagulant pharmacist long-range pager**:** **07623 905 674**

Medicines Information:
For questions relating specifically to the medicines (e.g. dosing, administration, interactions etc)
Medicines Information 02920 742979 WelshMedicines.Information@wales.nhs.uk

Atrial fibrillation: stroke risk assessment and antithrombotic treatment recommendation

Patient Addressograph		Consultant/GP: Directorate/Practice: Date:

- All patients with AF should undergo a **CHA_2DS_2-VASc stroke risk assessment (see over)**:

  CHA_2DS_2-VASc score: ☐

  - Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1
  - Offer anticoagulation to people with a CHA_2DS_2-VASc≥ 2:
  - CHA_2DS_2-VASc = 0: low risk – do not anticoagulate or offer anti-platelet unless other risk-factors are present

- Where oral anticoagulation is offered, Warfarin is a suitable first-line option.
- All patients should have assessment of bleeding risk before starting antithrombotic therapy.

  - **HAS-BLED score > 3** indicates "high risk" – caution and regular review following initiation of antithrombotic therapy

HAS-BLED score: ☐ Document risk management plan if > 2

Calculated CrCl (Cockroft & Gault) : ☐ ml/min (see "Dose adjustments" below if < 50 ml/min)

Patient understands and agrees with decision to prescribe antithrombotic medication (tick box)
Patient understands risks and benefits of antithrombotic medication (tick box) ☐
Patient has signed a completed counselling checklist (for DOAC) and this has been filed in their notes. (tick box) ☐
Patient has received the appropriate educational booklet and warning card (tick box) ☐

Choice of antithrombotic medication (tick box):

Apixaban 2.5mg BD	☐	Apixaban 5mg BD	☐
Dabigatran 110mg BD	☐	Dabigatran 150mg BD	☐
Edoxaban 30mg OD	☐	Edoxaban 60mg OD	☐
Rivaroxaban 25mg OD	☐	Rivaroxaban 20mg OD	☐
Warfarin – INR range (2.0-3.0)	☐		

Secondary care: Prescription for initiation of DOAC for AF should be accompanied by this form, fully completed.
Primary and secondary care: It is recommended that a copy be placed in the patient's medical record.

Dr's Name (Block letters)	Signature	Bleep no / Ext	Date

CHA_2DS_2-VASc score and stroke rate				
Risk factor	Score		Total score	Stroke (% / year)
None	0		0	0
Heart failure / LV dysfunction	1		1	1.3
Hypertension	1		2	2.2
Age ≥ 75	2		3	3.2
Diabetes mellitus	1		4	4.0
Stroke / TIA / thromboembolism	2		5	6.7
Vascular disease	1		6	9.8
Age 65 - 74	1		7	9.6
Female	1		8 - 9	6.7 – 15.2

HAS-BLED bleeding risk score		
	Clinical characteristic	Points
H	(Uncontrolled) Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding history[1]	1
L	Labile INRs[2]	1
E	Elderly (age > 65 years)	1
D	Drugs[3] or Alcohol[4] (1 point each)	1 or 2
	Total score (Maximum 9 points)	

[1] Bleeding history – recent GI bleed / active GI ulcer disease. Recent surgery. Recent ICH. Coagulation or platelet disorder

[2] Labile INR – unstable / high INRs or poor time in therapeutic range (e.g. < 60%)

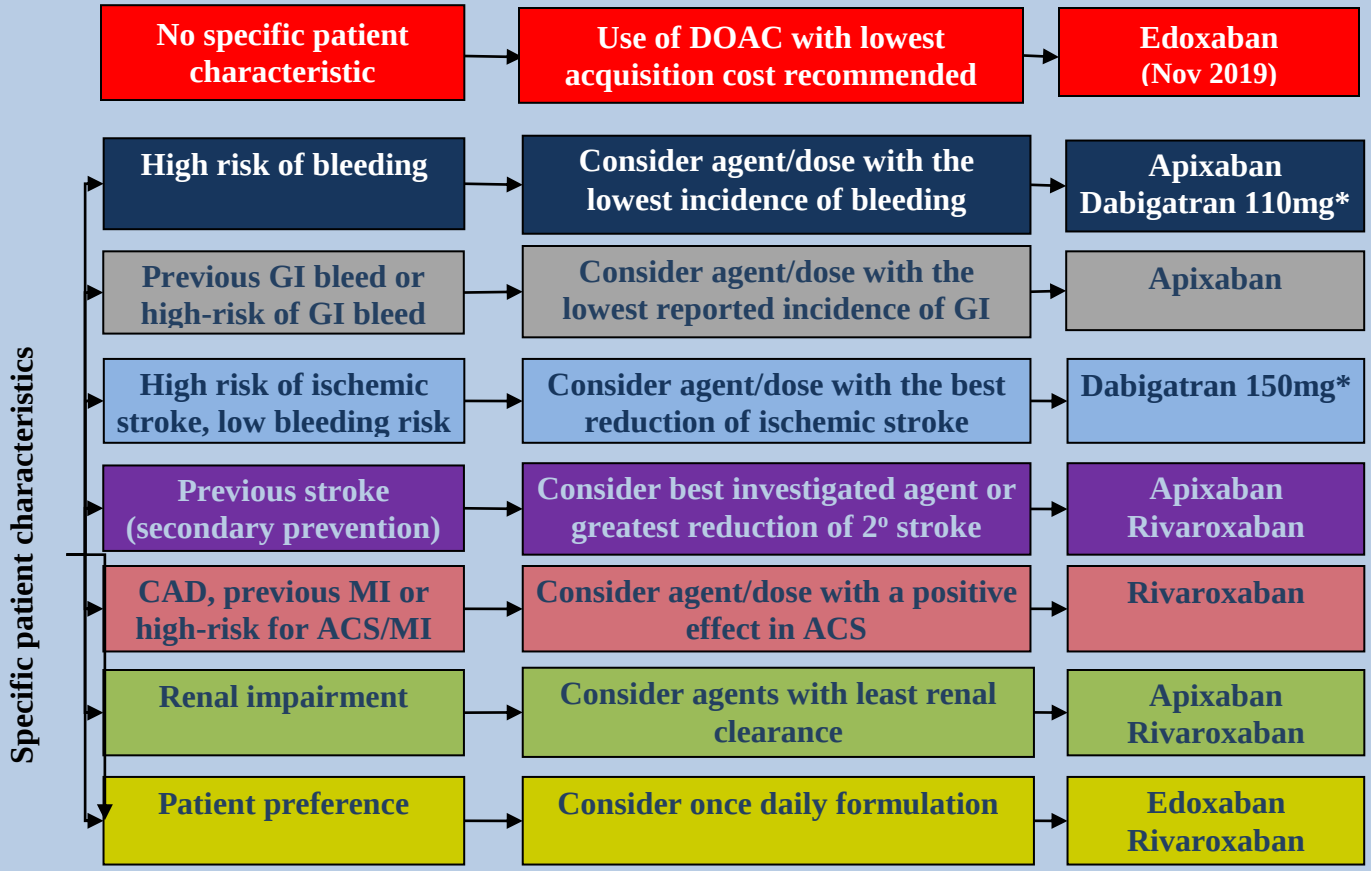
[3] Drugs – aspirin, clopidogrel, other antiplatelet agent or NSAIDs

[4] Alcohol – excess consumption

References:

- NICE guideline CG180. Atrial fibrillation. http://www.nice.org.uk/guidance/CG180
- Ideal body weight calculator at: http://clincalc.com/Kinetics/IdealBW.aspx
- Creatinine clearance calculator at http://microguide.horizonsp.co.uk/viewer/cavuhb/adult
- Updated European Heart Rhythm Association, practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary Europace. 2015 Oct; 17(10):1467-507
- NICE Patient Decision Aid https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-patient-decision-aid2
- Atrial fibrillation: medication options http://optiongrid.org/option-grids/grid-landing/78

CAVUHB Guidance for choice of DOAC in patients with NVAF



*Licensed antidote available at UHW / UHL for dabigatran