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| **DOAC Review for Non-Valvular Atrial Fibrillation (NV-AF) Frequently Asked Questions** |

**What is non-valvular atrial fibrillation (NV-AF)?**

* The most recent European Society Cardiology guidance on AF (2016) suggests replacing the historic term ‘non-valvular’ AF with reference to the specific underlying conditions.
* The term “Valvular AF" refers to patients with mitral stenosis (moderate or severe) or mechanical heart valves and such patients should be considered only for warfarin therapy for stroke prevention.
* The term “Non-valvular AF” therefore encompasses cases of AF in the absence of the above.
* Biological valve replacements, or other valvular heart conditions, such as mitral regurgitation, mild mitral stenosis, aortic stenosis, and aortic regurgitation, do not tend to result in conditions of low flow in the left atrium, and therefore are not thought to further increase the risk of thromboembolism brought by AF. This group of patients, when it comes to choice of oral anticoagulation, can also be included   under the term non-valvular.

**Is Edoxaban as good as the other DOACs?**

* The rebate on Edoxaban is in place for five years.
* The manufacturers of other DOACs have not reduced the price or offered     sufficient rebates to review the decision of Edoxaban.
* A further review will only be considered if clinical evidence emerges that another DOAC is more effective and/or safer than Edoxaban; in the unlikely   event of a very significant price change of an equivalent product; or when a generic DOAC is available.

**Which patients should not be on Edoxaban?**

* Creatinine clearance <15ml/min – these patients should be on warfarin and DOACs should not be initiated.
* Creatinine clearance <30ml/min. Edoxaban or other DOAC should be started only after specialist advise.
* Edoxaban should not be used if the patient’s creatinine clearance is greater than 95ml/min Rivaroxaban should be considered in such patients if there are no contraindications.
* Metallic heart valves – warfarin is recommended for these patients.
* DOACs should not be considered if patients body weight >150Kg, pregnant, breastfeeding or planning pregnancy.
* Specialist advise should be obtained in patients with bleeding disorder, antiphospholipid syndrome, and body weight in between 120-150Kg.

**How do I convert patients to Edoxaban?**

* If patients meet the criteria for Edoxaban and have agreed to the change, they should be issued with a prescription for Edoxaban.
* They should be advised to use up the supply of existing DOAC before starting Edoxaban. They should start Edoxaban the day after they    use up their existing supply.
* If they are converting from Apixaban they should take both the morning and evening dose on the day before starting Edoxaban.
* Edoxaban should be taken once daily. The precise time of day is not important, neither is the timing in relation to food. The patient should decide the most convenient time of day for them. It is important to take Edoxaban every day at the same time.
* Community pharmacists are being informed of this change and will be supplied with all the relevant support materials.

**Why are we excluding patients who have creatinine clearance <30ml/min from an automatic change to Edoxaban and suggesting that if Edoxaban is considered it should be on specialist advice?**

* There is limited evidence as to which DOAC performs best in patients who have a creatinine clearance <30ml/min.
* The first line anticoagulant for patients with NV-AF who have a creatinine clearance <30ml/min is warfarin however DOACs can be used, if clinically indicated, if the creatinine clearance is 15-30ml/min.
* Because of the limitations of evidence in this group, if a patient has a creatinine clearance of 15-30ml/min and is on a DOAC it is best to refer for specialist advice if Edoxaban is envisaged.

**What happens if renal function changes?**

* Patients with a creatinine clearance <15ml/min should not be on a DOAC.  These patients should receive warfarin
* If renal function decreases significantly then the DOAC dose may need to be reviewed.
* For Edoxaban the important value for review of treatment is 50ml/min which should trigger a dose reduction to 30mg once daily.
* If the creatinine clearance is <30ml/min it may be appropriate to use Edoxaban, but this should only be done on specialist advice as these patients were excluded from clinical trials.
* Edoxaban and other DOACs are not recommended if the creatinine clearance is <15ml/min. These patients should receive warfarin if there is a clinical indication for long-term anticoagulation.

**Do I need to use the Cockcroft-Gault equation to estimate renal function, or can I use eGFR?**

* Alternatively, if a reduced dose of a DOAC has been started during an acute impairment of renal function, then the dose will need to be reviewed if renal function subsequently improves.
* All DOACs require a dose adjustment based on renal impairment.
* Cockcroft-Gault equation is the standard method for estimating creatinine clearance (CrCl) and drug dose adjustment in adults for starting and dose adjustment of DOACs. It is recommended by the manufacturers of all Direct Oral Anticoagulants (DOACS – Edoxaban, Rivaroxaban, Apixaban and Dabigatran) for determining kidney function of patients when prescribing these agents.
* The Cockcroft-Gault equation is the preferred method particularly for patients >75 years old (see BNF recommendation).
* Studies have demonstrated that use of the Cockcroft-Gault equation allows appropriate dosing of DOACs and minimises the risk of over anticoagulation.

**How often do I need to check weight and renal function?**

* Estimated glomerular filtration rate (eGFR) should not be used, as data suggests this can lead to inappropriate dosing in up to 50% of patients.
* DOAC should not be initiated if patient’s weight is greater than 150kg. If the patient’s weight is between 120-150Kg specialist haematologist opinion should be obtained before initiation of DOACs.
* Weight and renal function should be checked at initiation of treatment or when converting DOACs.
* Renal profile should be checked annually, if CrCl > 60ml/min with FBC and LFTs, 6 monthly review if CrCl 30-60ml/min and/or aged >75 years and/or frail and 3 monthly review of renal profile if CrCl 15-30ml/min.
* For new patients and those moving to Edoxaban, the dose should be reduced to 30mg once daily if the creatinine clearance is <50ml/min or if the patient weighs less than 60kg.

**What about patients with Liver disease?**

* Caution when prescribing any other new medicines which may interact with Edoxaban and require the dose of Edoxaban to be reduced to 30mg once daily - ciclosporin, dronedarone, erythromycin or ketoconazole
* All DOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk and are not recommended in patients with severe hepatic impairment.
* Liver function tests are recommended prior to treatment for those patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN.
* Edoxaban should be used with caution in patients with mild to moderate hepatic impairment.

**What drugs interact with Edoxaban and what should I do about them?**

* Periodic monitoring of liver function is recommended if treatment continues beyond one year.
* The dose of Edoxaban should be reduced to 30mg daily if the patient is taking any of the following medicines - ciclosporin, dronedarone, ketoconazole or erythromycin (when erythromycin is started the dose reduction to Edoxaban 30 mg should be done immediately and the same is true in reverse. In other words, no ‘lag’ time required). This is irrespective of renal function and weight. See Edoxaban SPC for further details.
* If you have a patient already on a lower dose due to either weight or renal function, there is no further dose reduction required in relation to the above interacting drugs therefore if a patient is already on 30mg then do not reduce to 15mg.
* As with other anticoagulants, the risk of bleeding is increased if Edoxaban is used in combination with one or more antiplatelet drugs. This combination is clinically appropriate in certain circumstances, but this should only be done on the advice of a specialist and a clear treatment plan describing the intended duration of treatment.
* A proton pump inhibitor should be considered along with Edoxaban or other DOAC if the patients age is greater than 75.

**Can Edoxaban go into a patient compliance device?**

* There are no known issues with using Edoxaban in a compliance device.

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| Contact for This Policy   | The Cardiology & Anticoagulation Working Group Via medicine.question@dorsetccg.nhs.uk   |