Specialist Pharmacy Service

NHS

Direct Acting Oral Anticoagulants (DOACs) in Renal Impairment : Practice Guide To Dosing Issues

The first stop for professional medicines advice

Audience:

Non-specialist health care professionals responsible for prescribing or for reviewing patients requiring oral anticoagulant medicines. It is intended particularly for new or less experienced practitioners working in primary care settings.

Purpose:

To explain the background to dosing decisions for DOACs in patients with impaired renal function and provide case study examples illustrating the implications of such decisions. There are currently uncertainties in this field and a range of individual patient factors to consider. This document is intended as a practice aid not national guidance.

Summary:

It is important to consider renal function (i.e. to 'think kidneys') when selecting the dose of any DOAC for each individual patient. The usual measure of renal function (estimated Glomerular Filtration Rate (eGFR)) is not generally recommended for DOAC dosing decisions. In the major clinical trials of patients with non-valvular Atrial Fibrillation (AF) dosage was based on estimates of renal clearance based on the Cockcroft and Gault (CG) equation. This is not the same as the eGFR reported by most pathology services. This document signposts useful resources when making clinical decisions about DOAC dosing in renal impairment and provides case study examples from current clinical practice.

Contents

Background to dosing of DOACs in renal impairment

DOACs offer an alternative treatment option to warfarin in the management of patients with thromboembolism (VTE) and non-valvular AF.

One advantage of DOACs over warfarin is the lack of any requirement to regularly monitor clotting parameters with consequent dosage adjustment. This is because DOACs are given as fixed once or twice daily regimens. However, they are all dependent on the kidney for excretion (see table 1) and may require dose modification depending on the patient's renal function.

Table 1: Renal clearance for DOACs[1]

Drug	Renal clearance
Apixaban	27%
Dabigatran	80%
Edoxaban	50%
Rivaroxaban	35%

These documents explain key issues in the measurement of renal function and medicine dosages:

- The effect of renal function on the dosage. LINK
- The method used to assess renal function to make an appropriate dosage choice. LINK

An incorrect DOAC dose may have important efficacy and safety implications:

- Using a lower dose when patients do not meet the criteria for dose reduction may increase the risk of embolic events and result in potentially preventable strokes.
- Using a higher dose where the renal function indicates that a dose reduction is necessary may increase the risk of bleeding. [2,3,4,5]

Anticoagulation is generally prescribed for older patients. A recent audit in primary care reported 4 in 5 patients taking anticoagulants were aged 65 or over and 1 in 2 were aged 75 or over.[6] The risk of developing kidney disease also increases with age, so DOACs are likely to be prescribed for a substantial number of people who will require dosage adjustment. Regular monitoring to identify and address the consequences of any deterioration in kidney function over time is also important.

Which measures of renal function are used in practice to guide dosage adjustments?

In the UK, eGFR is widely reported by NHS pathology services and provides an estimate of renal function. It is used in the classification and staging of chronic kidney disease (CKD). The British National Formulary (BNF) advises that for most drugs and for most adult patients of average build and height, dosage adjustments based on eGFR are acceptable. However when prescribing high risk drugs, or for the elderly, or for patients at extremes of muscle mass, the calculation of creatinine clearance (CrCl) is recommended to support dosing decisions. [7]

Which measure of renal function should be used to guide dosage adjustments for DOACs?

The BNF currently advises that dosage adjustments for DOACs should be based on CrCl. The licensed doses for all DOACs also currently use CrCl to estimate renal function. Dosages are given in the manufacturers' summary of product characteristics. LINK

As well as reflecting the product license, use of the CG equation to guide DOAC dosage reflects the dosing regimens used in the clinical trial programmes in non-valvular AF patients. For edoxaban and rivaroxaban actual bodyweight was used in the calculation.[8, 9] Apixaban dosing is determined by the following parameters: age, actual body weight and serum creatinine. A dose reduction to 2.5mg twice a day is recommended only if two of the three parameters are present or for patients with a CrCl below 30ml/minute.[10]

Although dabigatran does not use CrCl specifically to guide dosage, clinical trial exclusions included a CG estimated CrCl of less than 30 ml/minute. Current advice is to consider using the lower dosage (110mg twice a day) if the CrCl is between 30-50 ml/minute, taking into account bleeding risks.[11]

Extremes in body mass present another complexity in dosing of DOACs. There are limited data on appropriate dosing in such patients and the CG equation may not be accurate for estimation CrCl at extremes of bodyweight, especially in obese patients LINK. If unsure always seek specialist advice.

Guidelines for clinical practice

A recent editorial in the Drug and Therapeutics Bulletin outlines the debate relating to the dosing of DOACs in renal impairment and how this should be evaluated. A case is made for national guidance on DOAC dosing to help clinicians prescribe these drugs safely and effectively, particularly in patients with renal impairment.[12]

There are many guidelines currently available to support dosing decisions, ranging from International Society guidance[1, 13] to more locally produced documents.

The NICE guideline for Chronic Kidney Disease (section 1.6.17) advises that apixaban should be considered in preference to warfarin in patients with a confirmed eGFR of 30-50 ml/min/1.73m^2 and AF LINK but the criteria for a dose reduction of apixaban (two out of three of age ≥ 80 years, weight ≤ 60kg or serum creatinine ≥ 133 micromol/l or a creatinine clearance of 15-29 ml/minute) still applies for dose selection.

Some example guidelines are given on the following page. The list is not exhaustive; examples are included to give readers a flavour of the available guidance. All of these guides use CrCl for dosing recommendations. Readers should also refer to the guidelines in their own locality.

Examples

MGP Limited Guideline LINK
Produced by a multidisciplinary panel of clinicians encompassing nephrology, cardiology, haematology, stroke, general practice and renal pharmacy expertise (2018):
Non-vitamin K oral anticoagulation options for patients with non valvular AF and renal impairment.
[Development of this guideline was commissioned and funded by Bayer but it is clearly stated in the document that the views and opinions are those of the contributors.]

North West Coast Strategic Clinical Network LINK
Consensus statement on how to calculate the Creatinine Clearance (CrCl) which is necessary when assessing the Dose of Direct-Acting Oral Anticoagulants (DOACs) 2018.

NHS Greater Glasgow and Clyde LINK
DOAC Prescribing in Patients with Non-Valvular AF and for the treatment and prevention of VTE. Frequently Asked Questions. March 2018.

NHS Dudley LINK
Briefing on New Oral Anticoagulants January 2019 (update).

Canterbury and Coastal CCG: East Kent Prescribing Group LINK
Anticoagulation in AF guidance May 2018 monitoring (amended) v2.

Pan-London AF Programme, Imperial College Health Partners et al LINK
AF toolkit Detect, Protect and Perfect. The authors recommend the use of CrCl for estimating renal function whilst highlighting the limitations of this in patients at extremes of body weight (less than 50kg or more than 120kg) where there is limited data on the use of DOACs. It includes the recommendations from South East London Area Prescribing Committee (2017) on how to calculate CrCl for patients prescribed DOACs. LINK

Some case examples of dosing of DOACs in AF and the rationale for choice of dosage are given in appendix 1.

Tools for calculating creatinine clearance in clinical practice

Although clinicians can calculate CrCl using the CG equation, many practitioners in primary care utilise tools embedded in their clinical systems (e.g. EMIS, SystmOne and Vision) for this.
These are simple to use as they pull the patient's clinical parameters directly into the CG calculation from the clinical system. (NB It is very important to ensure that up-to-date values are being used, particularly for weight and creatinine). However, experts have questioned the use of these embedded tools LINK when deciding on DOAC doses due to adjustments from actual to ideal body weight within the CG calculator. Instead the use of a web based application such as MDCalc LINK is suggested where actual bodyweight is used to calculate the CG CrCl. If in addition the patient's height is added the different weight method calculations (modified for body weight) can be seen giving a range of possible values for CrCl. Where these results cross or are close to a CrCl level that may require a dose change this can support the clinician making a dosing decision.

Always remember that the CrCl is an estimate and should not be considered in isolation. Decisions on dosing should always take into account the renal function in conjunction with an estimate of stroke risk and bleeding risk with anticoagulation - as recommended by NICE LINK .

Stroke risk estimation: use the CHA_2DS_2VASc score. A higher score = higher stroke risk.

Bleeding risk estimation: use a score such as HAS-BLED and address any modifiable risk factors. A higher score = higher bleeding risk**.**

Frequency of monitoring renal function in patients prescribed DOACs

Renal function should be assessed at baseline in all patients starting a DOAC.[1] Although no specific recommendations are made by manufacturers on the frequency of monitoring, the importance of monitoring renal function was highlighted by the MHRA as early as 2012. LINK

The current consensus is that renal function should be assessed at least once a year.[1] More frequent monitoring is required in clinical situations where renal function may decline and in patients with impaired renal function at baseline.

The European Heart Rhythm Association suggests that if the CrCl is less than 60ml/minute, the frequency of monitoring (in months) can be guided by the CrCl divided by 10.[1] For example, if the creatinine clearance is 30 ml/minute then the renal function (and the prescribed dose) should be re-assessed every 3 months.

Conclusions

Selecting the correct dosage of DOAC for a patient requires careful consideration of renal function. Pharmacy teams are ideally placed to play a key role in both primary and secondary care in ensuring the safe prescribing, on-going monitoring and appropriate dosage adjustments of DOACs in everyday clinical practice.

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Appendix 1: Examples of dosing DOACs in AF (stable renal function)

Scenario	Recommendations
Is this the correct dose of RIVAROXABAN? 76 year old male. 63kg. Creatinine 117 micromol/l, eGFR 52 Currently prescribed rivaroxaban 20mg once a day **CrCl calculated using actual body weight is 42 ml/minute**	**Plan** Reduce dose of rivaroxaban to 15mg once a day **Rationale** CrCl is less than 50 ml/minute (despite eGFR above 50)
Is this the correct dose of APIXABAN? 83 year old male. 74kg Creatinine 78 micromol/l, eGFR 57 Currently prescribed apixaban 2.5mg twice a day **CrCl calculated using actual body weight is 66 ml/minute**	**Plan** Increase dose of apixaban to 5mg twice a day **Rationale** Creatinine clearance is above 30 ml/minute and only one factor is present (age) for dose reduction to the lower dosage (two or more needed before reducing the dose)
Is this the correct dose of DABIGATRAN? JG 83 year old female. 51kg Creatinine 99 micromol/l, eGFR 47 Currently prescribed dabigatran 110mg twice a day **CrCl calculated using actual body weight is 31 ml/minute**	**Plan** Switch to an alternative DOAC **Rationale** Although this is a licenced dosage dabigatran is contra-indicated if the CrCl less than 30 ml/minute There is limited data on the use of DOACs in severe renal impairment however with a CrCl of 15-30 ml/minute this could be changed to either apixaban 2.5mg twice a day or edoxaban 30mg once a day or rivaroxaban 15mg once a day
Is this the correct dose of EDOXABAN? 66 year old female. 86kg Creatinine 72 micromol/l, eGFR 78 Currently prescribed edoxaban 60mg once a day **CrCl calculated using actual body weight is 92 ml/minute**	**Plan** Continue current dose of edoxaban **Rationale** Dose reduction of edoxaban is only recommended if the weight is less than 60kg and/or the CrCl is 15-50 ml/minute or with specific drug interactions

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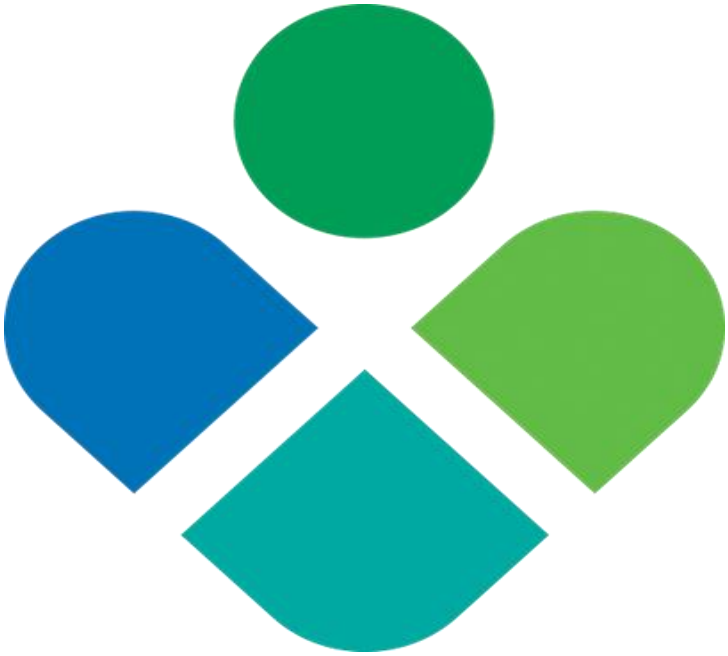

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