Practice guide to dosing of direct acting oral anticoagulants in patients with renal impairment

The first stop for professional medicines advice
Summary

The dose of direct acting oral anticoagulants (DOACs) recommended depends on the indication, concomitant medication and a number of individual patient factors.

The dose prescribed should be in line with licensed recommendations to reduce both the risk of thromboembolic events and bleeding complications.

All of the DOACs are renally excreted so dose selection and modification may be necessary in patients with renal impairment. The choice of dose is guided by creatinine clearance (CrCl) using the Cockcroft and Gault equation.

It is important to note that:

- Creatinine clearance is not the same as the estimated glomerular filtration rate (eGFR) which is reported by most pathology services and is used to stage levels of chronic kidney disease.

- The Cockcroft and Gault (CG) equation has limitations in application.

- In the landmark clinical trials for atrial fibrillation actual bodyweight was used to estimate creatinine clearance. There is debate, particularly in patients that are overweight, whether this is the best value to use when estimating creatinine clearance.

- There are a number of clinical tools available – web based and in primary care prescribing systems – that may be used for the CrCl calculation. They do not all use the same methodology for weight in the equation and may give different answers for the CrCl estimate.

This paper focusses on the use of DOACs in the atrial fibrillation cohort – a cohort where published and local audit data have shown that the correct selection of dose is important to achieve desired outcomes but that dosage errors are not uncommon in everyday practice. This may lead to increased bleeding and/or failure to achieve the level of stroke risk reduction for which the DOAC was prescribed.

This paper will be useful to medical and non-medical prescribers and the wider pharmacy community working in both primary and secondary care who will prescribing or checking the dose of DOAC prescribed for their patients.

The resource discusses dosing in renal impairment (excluding dialysis patients and patients with a CrCl less than 15 ml/minute), limitations of the CG equation and illustrates some of the creatinine clearance calculation tools available. Real life examples are given to illustrate the implications for dose selection.

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 where necessary dose adjustment of DOACs.
Background to Dosing of DOACs in Renal Impairment

The direct/novel oral acting anticoagulants (DOACs/NOACs) offer an alternative treatment option to warfarin in the management of patients with thromboembolism and non-valvular atrial fibrillation (AF). This paper will focus on dosing of the DOACs in patients with AF.

One advantage of these medicines over warfarin is that they do not require monitoring of clotting parameters with consequent dosage adjustment as they are given as fixed once or twice daily regimes. 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>27%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>80%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>50%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>35%</td>
</tr>
</tbody>
</table>

The UK doses licensed for AF for each of these medicines is shown in Appendix 1. It is important to note the choice of dosage is based on an estimate of renal clearance using the Cockcroft and Gault (CG) calculation for creatinine clearance (figure 1). Creatinine clearance using the Cockcroft and Gault equation is not the same as the estimated glomerular filtration rate (eGFR) which is reported by most pathology services and if the eGFR is used this may overestimate renal clearance particularly in elderly patients with low body weight/body mass index.

Figure 1: Cockcroft and Gault equation

Cockcroft and Gault Creatinine Clearance (CrCl) can be calculated by:

\[
CrCl = 1.23 \text{ (male)/1.04 (female)} \times (140 - \text{age in years}) \times \text{weight (kg)} / \text{Creatinine (micromol/l)}
\]

Limitations to the use of the Cockcroft and Gault equation include:
- Should not be used in unstable renal function/acute kidney injury/rapidly changing renal function
- Not suitable for children or in pregnancy
- Not suitable in patients who are very oedematous
- Extremes of body weight may over estimate clearance
- In patients with muscle wasting may over estimate creatinine clearance
- Patients with limb amputation

Any equation using creatinine is subject to inaccuracies in acute renal impairment and in practice clinicians need to look at trends, clinical parameters such as urine output, individual drug properties and make a judgment on reducing or withholding doses on an individual patient basis.
Use of the CG equation to guide initial dosage reflects the dosing regimens used in the clinical trial programme in non-valvular AF patients for edoxaban\(^9\) and rivaroxaban\(^\text{10}\) with actual bodyweight being used in the calculation. Apixaban used a combination of age, actual body weight and serum creatinine for choice of dosage\(^\text{11}\) and recommends using the reduced dosage (2.5mg twice a day) in patients with a creatinine clearance below 30ml/minute.\(^5\)

Although dabigatran does not use the creatinine clearance specifically to guide dosage, clinical trial exclusions included a CG estimated creatinine clearance of less than 30 ml/minute and current advice is to consider using the lower dosage (110mg twice a day) if the creatinine clearance is between 30-50 ml/minute taking into account the bleeding risks.\(^\text{2,12}\)

These dosing recommendations are established in the product licence of each drug (appendix 1) and national and international guidelines.\(^\text{13}\)

Using the Cockcroft and Gault equation for dosing of DOACS and Body Weight

In the DOAC trials actual body weight was used to calculate creatinine clearance. However median weight of the patients was in the region of 83kg and there is limited data from the AF clinical trial programme with DOACs in patients who are at extremes of bodyweight (less than 50kg or more than 120kg).\(^\text{9,10,11,12}\)

In 2016 the International Society for Thrombosis and Haemostasis published a guideline paper summarising the data on DOACs in obese patients recommending standard dosing if the BMI is less than or equal to 40kg/m\(^2\) and weight less than or equal to 120kg and to avoid use above these levels (or to consider drug specific peak and trough levels if available).\(^\text{14}\)

‘Accuracy’ of the CG equation in extremes of bodyweight is uncertain and there is a concern that using actual body weight for patients who are overweight may overestimate creatinine clearance. This has led to debate of the choice of weight to use within the CG equation when selecting a DOAC dose and examples of guidelines reflect this uncertainty.

The South East London\(^\text{15}\) guide suggests:

- Use actual body weight if the body mass index (BMI) is less than 30kg/m\(^2\).
- In patients who are obese/morbidly obese (BMI\(\geq\) 30kg/m\(^2\)) calculating the creatinine clearance using both ideal body weight and adjusted body weight (which assumes some of the excess weight is muscle) to give a range of estimates for creatinine clearance from which a clinical decision can be made on choice of dosing for the individual patient.

**Ideal body weight**

Males = 50kg + 2.3kg for every inch in height above 5 foot (60 inches)
Females = 45.5kg + 2.3kg for every inch in height above 5 foot (60 inches)

**Adjusted body weight**

Adjusted body weight = ideal body weight + 0.4 x (actual body weight – ideal body weight)

More recently the North West Coast Strategic Clinical Network have produced a consensus statement on how to calculate the creatinine clearance when assessing the dose of DOAC recommending use of actual body weight (in line with the trial practices).\(^\text{16}\) However it does not discuss what to do at extremes of bodyweight or whether to avoid using the DOACs where there is this uncertainty.
Other guides have suggested using adjustment for patients with a BMI ≥ 25 kg/m²

Use of web based applications that allow these adjustments offer a practical solution for clinical practice. MDCalc is an example of a web based application for creatinine clearance. https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation. In this tool actual bodyweight is used in the result for creatinine clearance, original CG By including the patient’s height into the calculator the different weight method calculations can be seen (figure 2) giving a range of values from which to make a clinic judgement.

Figure 2: Creatinine Clearance Calculations Using the MDCalc Application

In primary care the commonly used GP prescribing systems have built in clinical tools to allow calculation of the CG creatinine clearance. Appendix 2 illustrates how to find these tools on EMIS, SystmOne and Vision. These are a useful resource but always ensure:

- Up-to-date clinical parameters are being used in particular weight and renal function.
- Be aware of the methods and the limitations to the methods used to calculate CrCl within these tools.
- Apply the caveats regarding weight as outlined above where the values are close to a recommended dose change adjustment the different methods of calculating of CrCl (figure 2). A clinical decision based on thromboembolic versus bleeding risk for the individual patient may be required.
Why does it matter?

Prescribing of DOACs outside of the licensed dose may have important efficacy and safety implications:

- Using the lower dose for patients that do not meet the criteria for dose adjustment may result in an increase in embolic events and result in potentially preventable strokes.

- Using the higher dose for patients whose renal function suggests a lower dose is indicated may have worse outcomes with respect to bleeding risk.

This has been seen in real life data outside of the clinical trial programme with particular concern over an increased risk of thromboembolic events thus highlighting the importance of correct dosage selection. In a recent CCG wide audit of DOAC dosing in the AF population on the south coast of England approximately one in nine patients already prescribed a DOAC for AF required an adjustment of dosage, mainly for renal function, highlighting that this is an important safety issue in everyday clinical practice.

Figures 3 and 4 give examples demonstrating the use of the CG equation for selecting DOAC dosage and why the debate over choice of weight used in the CG equation gives a dilemma for prescribers clinical practice.

Figure 3: Example of the Dosing Dilemma in Clinical Practice (CrCl shown in figure 2)

69 year old male patient with AF. Weight 120 kg, Height 185 cm, and BMI 35.1 kg/m^2
Renal function is stable with a creatinine of 160 micromol/l
Prescribed APIXABAN 2.5mg twice a day.
The GP has noted that this dose has been chosen because the patient has renal impairment.

**Is this the correct dose of APIXABAN?**
- Based on the licensed dose only 1 criteria for dose reduction is present.
- The licensed dose is 5mg bd

**What if an alternative DOAC had been prescribed?**
Using the actual body weight methodology the CrCl is 65 ml/minute. With this CrCl licensed doses for AF are rivaroxaban 20mg once a day or edoxaban 60mg once a day. For dabigatran either dose could be chosen.

However the patient is overweight and figure 2 shows the range of CrCl results seen if weight adjustments are used in the CG calculation illustrating that alternative CrCl calculations bridge the cut off point for adjusting the dose for both rivaroxaban and edoxaban in this scenario.

Clinical judgement on choice of dose should take into account:
- **Stroke risk** estimation using the CHA2DS2-VASc score. A higher score = higher stroke risk.
- **Bleeding risk** (using a score such as the HAS-BLED) and addressing any modifiable A higher score = higher bleeding risk.

You will also need to consider:
- What is the balance between stroke risk and bleeding risk?
- Are there any drug interactions that may affect your decision?
- Is the renal function stable?
• How often should I review the dose and the renal function?
• Are there any other co-morbidities that need to be considered?
• How will I discuss this with the patient?

Figure 4: Further examples from clinical practice (see appendix 1 for dosing information)

WC 76 year old male. 63kg. Stable renal function. Creatinine = 117 micromol/l, eGFR = 52. Prescribed dose of RIVAROXABAN = 20mg od. Calculated CrCl using actual body weight = 42 ml/minute. DOSE REDUCTION of RIVAROXABAN to 15mg OD recommended.

KS 83 year old male. 74kg. Stable renal function. Creatinine = 78 micromol/l, eGFR =57. Prescribed dose of APIXABAN = 2.5mg bd. Calculated CrCl using actual body weight = 66 ml/minute. DOSE INCREASE of APIXABAN in 5mg BD recommended (CrCr>30 ml/minute and only 1 factor for dose reduction present).

JG 83 year old female. 51kg. Stable renal function. Creatinine = 95, eGFR = 48 and prescribed dose of DABIGATRAN = 110mg BD. Calculated CrCl using actual body weight = 32 ml/minute. Recommend: More frequent monitoring and switching to less renally dependent DOAC. (There is limited data on use of DOACs if CrCl is less than 30ml/minute. Apixaban is the least dependent on renal function for excretion. Apixaban, edoxaban and rivaroxaban are all licensed for use if the CrCl is above 15 ml/minute).

FC 66 year old male. 115kg, height = 185cm, BMI = 33.6 kg/m². Creatinine = 72 micromol/l, eGFR > 95 and prescribed dose of EDOXABAN = 60mg od. Calculated CrCl using actual body weight = 145 ml/minute. Calculated CrCl using ideal body weight = 100.5 ml/minute. Calculated CrCl using adjusted body weight = 118.5 ml/minute. Consider choice of agent. ? Effect of clearance on potential efficacy of EDOXABAN.
Frequency of monitoring renal function in patients prescribed DOACs

Renal function should be assessed at baseline in all patients starting a DOAC.

During treatment it is recommended that renal function should be assessed at least once a year. More frequent monitoring will be required in clinical situations where it is suspected that the renal function may decline and in patients with baseline impaired renal function.

Although no specific recommendations are made by the manufacturers on the frequency this has been raised as a safety issue by the MHRA. The European Heart Rhythm Association suggest that if the creatinine clearance is less than 60 ml/minute that the frequency of monitoring the renal function can be guided by the creatinine clearance divided by 10.

- 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.

How to Identify Patients Requiring Dose Adjustment

Hospital pharmacists have access to the required clinical parameters and are ideally placed to ensure correct initial and on-going doses are prescribed taking into account the limitations of CG in acute/unstable kidney injury. Good documentation on transfer of care is essential.

In primary care practice based pharmacists can also ensure correct doses are selected at initiation and at each medication review. More systematic audit of the DOAC cohort should focus on ensuring the correct dose is prescribed for the indication in line with recommended doses (appendix 1).

It is important to remember not to treat these estimates of CrCl in isolation. There is a wider multi-disciplinary team involved in the care of patients and the opportunity for collaboration and case discussion between primary and secondary care and between specialists (e.g. haematology, cardiology, elderly medicine, nephrology etc) should not be overlooked.

Conclusions

All of the DOACS have dosing regimens that need renal function to be taken into account for selection of the correct dosage.

There are a number of clinical tools to estimate CrCl but there are limitations to their application particularly in patients at increased bodyweight.

In routine clinical practice prescribed DOAC doses are often inconsistent with the licensed dose. These prescribing patterns may lead to increased thrombo-embolic risk and increased bleeding complications for patients.

Pharmacy teams can play a key role in both primary and secondary care in ensuring the safe prescribing and on-going monitoring of DOACs and in liaising with other specialists in the wider multidisciplinary team.
Appendix 1

Licensed Doses for the DOACs for the Prevention of Stroke and Systemic Embolism in Patients with Non Valvular Atrial Fibrillation (NVAF) with Respect to Renal Function

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Standard Dose</th>
<th>Adjustment Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APIXABAN</strong></td>
<td>5mg bd</td>
<td>If two or more of the following factors are present: Creatinine ≥ 133 umol/l, age ≥ 80 years, weight ≤ 60kg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If the creatinine clearance is 15-29 ml/minute reduce dose to 2.5mg bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra-indicated if the creatinine clearance is less than 15 ml/minute</td>
</tr>
<tr>
<td><strong>DABIGATRAN</strong></td>
<td>150mg bd</td>
<td>If the creatinine clearance is 30-50 ml/min, or age 75-80 years or there are clinical risk factors for bleeding consider reducing dose to 110mg bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra-indicated if the creatinine clearance is less than 30 ml/minute</td>
</tr>
<tr>
<td><strong>EDOXABAN</strong></td>
<td>60mg od</td>
<td>If the creatinine clearance is 15-50 ml/minute or body weight less than 60kg or there is concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole reduce dose to 30mg od.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra-indicated if the creatinine clearance is less than 15 ml/minute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance (&gt;95 ml/minute) after a careful evaluation of the individual's thromboembolic risk and bleeding risk.</td>
</tr>
<tr>
<td><strong>RIVAROXABAN</strong></td>
<td>20mg od</td>
<td>If the creatinine clearance is between 15-49 ml/minute reduce dose to 15mg od</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra-indicated if the creatinine clearance is less than 15 ml/minute</td>
</tr>
</tbody>
</table>
Appendix 2

Clinical tools available in GP Primary Care Systems

*****Always ensure you are working with up-to date clinical parameters*****

SystmOne
The tool can be accessed from the ‘clinical tools’ tab and then selecting ‘renal disease calculations’
If the data is available in the GP record this will be automatically populated with the last recorded figure and the calculation will be made. This can be saved to the patient’s record. This tool uses IBW.
EMIS-WEB

EMIS-WEB has an imbedded template that estimates creatinine clearance. This tool uses actual body weight unless the patient’s weight is more than 20% over ideal body weight (in which case it automatically substitutes ideal body weight). This assumes a height is recorded.

Recently a statement was added above the equation in the template (see below) that states that using imbedded CG equation in overweight patients may underestimate CrCl and to use with caution.
VISION

In VISION select the calculators tab and then click other to give the Cockcroft and Gault option in the resulting box in Vision+.
References


14 Martin K et al
Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH
Journal of Thrombosis and Haemostasis 2016 14 1303-1313

15 South East London Creatinine Clearance Guide for DOACs July 2017

16 North West Coast Strategic Clinical Network Consensus Statement on how to calculate creatinine clearance which is necessary when assessing the dose of DOAC

17 Steinberg B, Shrader P, Thomas L et al
Off label dosing of non-vitamin K antagonist oral anticoagulation and adverse outcomes. The Orbit II AF registry
JACC 2016 68 (64) 2597-2604

18 Bronnum Nielsen P, Flemming Skjøth S, Sogaard M et al
Effectiveness and safety of reduced dose non-vitamin K antagonists oral anticoagulation and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study
BMJ 2017 356: j510 http://dx.doi.org.10.1136/bmj.j510

19 Yao X, Shah ND, Sangaralingham LR et al
Non-vitamin K antagonist oral anticoagulation dosing in patients with atrial fibrillation and renal dysfunction
JACC 2017 69 (23) 2779-2790

20 Warren A
Frequency of dose adjustment of DOACs in general practice (unpublished data)

NHS Specialist Pharmacy Service
www.sps.nhs.uk