Dosing for direct-acting oral anticoagulants in non-valvular atrial fibrillation

Creatinine clearance (CrCl) calculation

Cockcroft–Gault equation:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times \text{constant}}{\text{serum creatinine (µmol/L)}}$$

Constant = 1.23 for males; 1.04 for females.

MDCalc and some calculators built into practice systems* adjust for body weight (BW) in those with BMI ≥27 or 30 kg/m², providing CrCl values based on ideal, adjusted or actual BW. If the CrCl range crosses a direct-acting oral anticoagulant (DOAC) dosing threshold, then use clinical judgement to agree suitable DOAC dose.*

Do not use eGFR to guide DOAC prescribing as this can lead to inappropriate dosing in up to half of people.

*__EMIS__ system calculator – if BMI >27 kg/m² and not yet started DOAC, use the non-adjusted CrCl (actual BW CrCl value), rather than the ideal BW (IBW) CrCl. Once on DOACs, the EMIS calculator provides CrCl based on actual BW. Vision – use the inbuilt calculator. **SystmOne** use the MDCalc formula or be aware SystmOne calculator uses IBW if weight >120% of IBW, so actual values need to be added manually.

Whether to use actual, ideal or adjusted BW when calculating CrCl in heavier individuals remains controversial.

Seek guidance if BW <50 kg or >120 kg unless local guidance provided. Rivaroxaban – SmPC states no dose adjustment at extremes of weight. Some advise not to use DOACs if BW >120 kg or BMI >40 kg/m²; others recommend measuring peak and trough levels and, if in normal range for the drug, can continue.

MDCalc: www.mdcalc.com

DOAC drug interactions (AWMSG, 2020)

Drug	Action required
HIV protease inhibitors	Avoid with apixaban, dabigatran, rivaroxaban. No data for edoxaban
Ketoconazole, itraconazole	Avoid with apixaban, dabigatran, rivaroxaban
Voriconazole, posaconazole	Avoid with apixaban, rivaroxaban
Rifampicin, carbamazepine, phenytoin, phenobarbital, St John's wort	Avoid with dabigatran. Caution with apixaban, edoxaban, rivaroxaban
Dronedarone	Avoid with dabigatran, rivaroxaban
Ciclosporin, tacrolimus	Avoid with dabigatran
Amiodarone, clarithromycin, quinidine, posaconazole, ticagrelor verapamil	Caution with dabigatran

See dose reductions for edoxaban interactions overleaf.

Monitor renal function

Creatinine clearance	Frequency of renal monitoring*
>60 mL/min	Every 12 months
30–60 mL/min	Every 6 months
15–<30 mL/min	Dabigatran contra-indicated; at least every 3 months
Age ≥75 years or frail	At least every 6 months

*More frequent monitoring appropriate if values are variable, if advised by specialist or on nephrotoxic drugs.

Patient-specific characteristics when choosing a DOAC (AWMSG, 2020)

Characteristic	Consider agent with:
History of GI bleed or high risk	Lowest reported GI bleeding outcomes/adverse effects
High risk of ischaemic stroke, low bleeding risk and age <80 years	Best ischaemic stroke reduction
Previous stroke	Greatest secondary stroke reduction
CrCl 30–50 mL/min	Less dependence on renal excretion (apixaban 27%; rivaroxaban 35%; edoxaban 50%; dabigatran 80% [based on % clearance of total absorbed dose])
Known CAD, previous MI or high risk for ACS/MI	Positive effect in ACS
Patient preference	Once- or twice-daily formulations

ACS = acute coronary syndrome; CAD = coronary artery disease; GI = gastrointestinal; MI = myocardial infarction.

References

Nottinghamshire APC (2021) *Atrial fibrillation (non-valvular): prescriber decision support on anticoagulation*. bit.ly/3flWjMj

Surrey & NW Sussex APC (2020) *Calculating renal function (CrCl) when monitoring direct oral anticoagulants (DOACs) for safe and effective dosing of patients*. bit.ly/33BGCnT

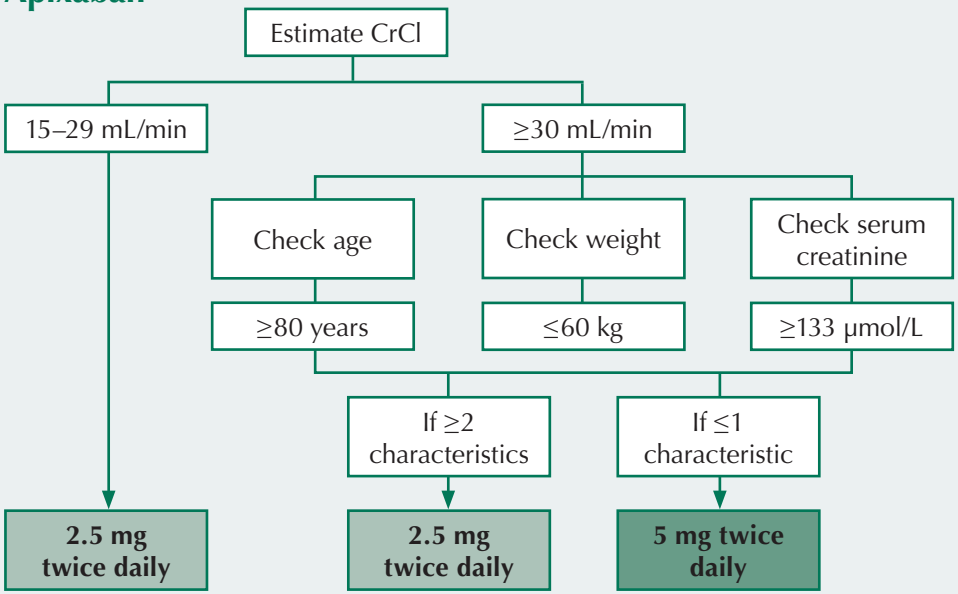
NHS Fife (2018) *Calculating creatinine clearance for DOACs*. bit.ly/3GQ88MR

All Wales Medicines Strategy Group (AWMSG) (2020) *All Wales advice on oral anticoagulation for non-valvular atrial fibrillation*. bit.ly/3FQKHS2

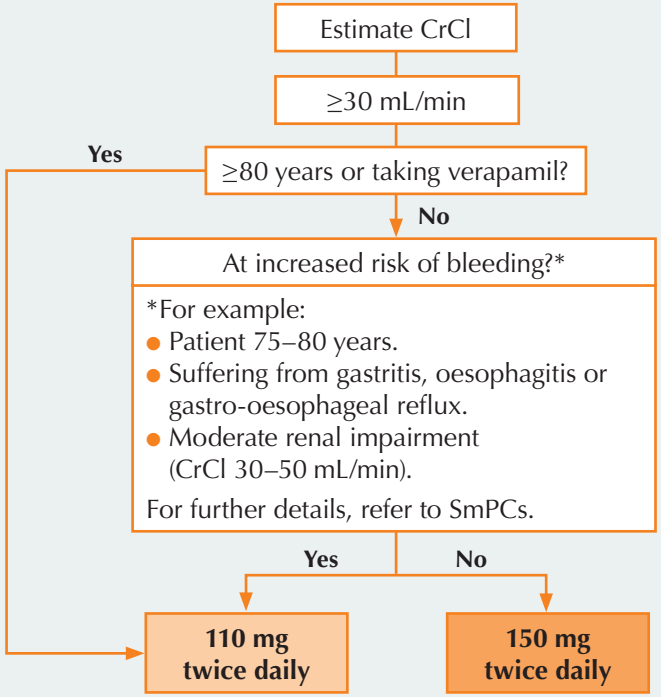
How to dose DOACs for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation

All the available DOACs are contraindicated/not recommended at creatinine clearance (CrCl) <15 mL/min. Dabigatran is contraindicated at <30 mL/min. Caution when using DOACs with drugs which may increase bleeding risk (e.g. aspirin, NSAIDs, SSRIs, SNRIs).

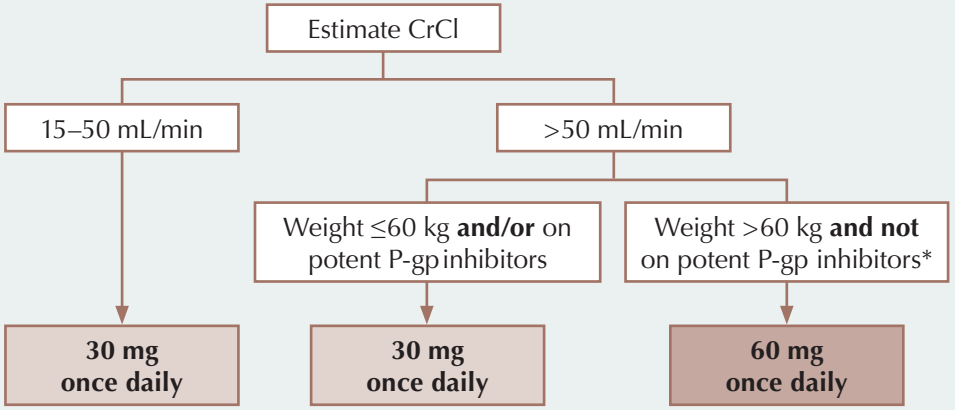
Apixaban



Dabigatran



Edoxaban

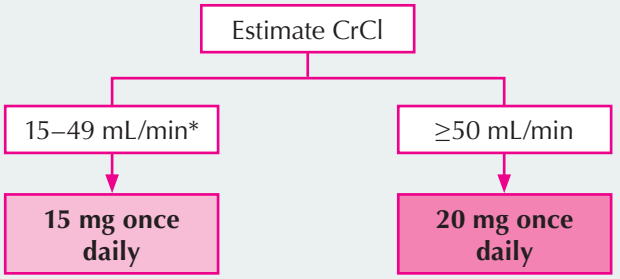


Decreased efficacy at high CrCl – evaluate use.

*Potent P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole.

Rivaroxaban

(Take with food)



Licensed for those with non-valvular atrial fibrillation and one or more risk factors: congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke or TIA.

*Rivaroxaban is to be used with caution in people with CrCl 15–29 mL/min.

Always consult the electronic BNF or the Summaries of Product Characteristics (SmPCs) prior to prescribing any drug.

SmPCs: Apixaban | Dabigatran | Edoxaban | Rivaroxaban

Authors: Yassir Javaid, GPwSI in Cardiology, Northampton; Pam Brown, GP, Swansea.
Citation: Javaid Y, Brown P (2022) Dosing for direct-acting oral anticoagulants in non-valvular atrial fibrillation. *Diabetes & Primary Care* **23**: [Early view publication]