Assessing kidney function in oral anticoagulant prescribing: an aid for safer drug and dose choices

Su Wood, Duncan Petty, Matthew Fay, Andrew Lewington

Authors

Su Wood
Practice-based Pharmacist, Prescribing Support Services, and PhD Student, University of Leeds

Windhill Green Medical Centre, 2 Thackley Old Road, Shipley, West Yorkshire, BD18 1QB

Duncan Petty
Practice-based Pharmacist, Prescribing Support Services, and Lecturer Practitioner, University of Leeds

Academic Unit of Medicines Management, School of Healthcare, Baines Wing, University of Leeds, Leeds, LS2 9JT

Matthew Fay
GP and GPwSI in Cardiology

Westcliffe Medical Practice, Westcliffe Road, Shipley, West Yorkshire, BD18 3EE

Andrew Lewington
Consultant Renal Physician

St James's University Hospital, Beckett Street, Leeds, LS9 7TF

Correspondence to:
Mrs Su Wood
(suei.wood3@bradford.nhs.uk)

Key words

aged, anticoagulant drugs, atrial fibrillation, chronic kidney disease, renal insufficiency

doi: 10.5837/bjc.2013.16

Br J Cardiol 2013;**20**:61–4

Incidence of stroke attributable to atrial fibrillation increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years. The use of oral anticoagulants to reduce the risk of stroke is well established, but all the available agents can cause bleeds if used in excess dose, in high-risk patients or in patients with reduced kidney function.

This article highlights the need to assess kidney function as stated in the newly published European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC) practical guide on the use of the new oral anticoagulants (NOACs).[1] The EHRA guide has a section on NOACs for patients with chronic kidney disease (CKD) where it is stated that "a careful follow-up of renal function is required in CKD patients, since all (NOACs) are cleared more or less by the kidney". It continues "in the context of NOAC treatment, creatinine clearance is best assessed by the Cockcroft method, as this was used in most NOAC trials".

The authors discuss the issues and present a simple guide on why and how to use the Cockcroft Gault equation for kidney function estimation. They also note that for drug and dosing decisions, reduced kidney function, for whatever reason (not just where a patient has been assessed as having CKD), needs to be assessed to reduce the risk of harm.

Introduction

Atrial fibrillation (AF) is an epidemic of our time, with prevalence increasing from 0.5% at age 50–59 years to almost 9% at age 80–89 years.[2] AF predisposes to stroke and thromboembolism with an approximately five-fold greater risk than that of people without AF; the incidence of strokes attributable to AF increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years.[2]

The use of anticoagulants to reduce the risk of stroke in AF is well established.[2] Three new 'novel oral anticoagulants' (NOACs) are now licensed for stroke reduction in AF as alternatives to the coumarins (e.g. warfarin) and have been approved by the National Institute for Health and Clinical Excellence (NICE):[3-5] dabigatran,[6] a direct thrombin (IIa) inhibitor, rivaroxaban[7] and apixaban,[8] both Xa inhibitors. These agents have a more stable dose response than warfarin but are dependent on renal clearance; dose modification is recommended in patients with reduced kidney function. The population most in need of anticoagulation to reduce the risk of AF-related stroke is generally older with multiple manifestations of cardiovascular disease, so chronic kidney disease (CKD) is likely.

Used correctly, NOACs are at least as safe as well-controlled warfarin. Like warfarin they can cause bleeds, especially if used in excess doses, in patients with higher risks for bleeds, and in reduced kidney function. A number of cases of serious and

Box 1. Medicines and Healthcare products Regulatory Agency (MHRA) dabigatran advice for healthcare professionals[9]

Renal function should be assessed in all patients before starting dabigatran, and at least once a year thereafter in patients older than 75 years or in any patient with a suspected decline in renal function.

New dabigatran advice for healthcare professionals:

- Do not start dabigatran in any patient with severe renal impairment (creatinine clearance <30 ml/min)
- Assess renal function:
  - in all patients before starting dabigatran
  - when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, or with some co-medications)
  - at least annually in patients older than 75 years
  - at least annually in patients with renal impairment

Check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs.

Figure 1. Dosing in reduced kidney function chart

Anticoagulants for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Drug use and dosing based on kidney function estimation (estimated creatinine clearance [eCrCl])

CrCl >50 ml/min	**Any anticoagulant** – no dose adjustment needed based on kidney function
CrCl 30–49 ml/min	**Apixaban** 5 mg twice daily or 2.5 mg twice daily if serum creatinine (SCr) ≥133 μmol/L with age ≥80 years or body weight ≤60 kg **Dabigatran** 110 mg twice daily if high risk of bleeding (suggest use of HAS-BLED score to assess risk); otherwise 150 mg twice daily **Rivaroxaban** 15 mg once daily **Warfarin** International normalised ratio (INR) dependent dose adjustment
CrCl 15–29 ml/min	**Apixaban** 2.5 mg twice daily **Dabigatran** contraindicated **Rivaroxaban** 15 mg once daily but caution – plasma concentrations significantly increased (average 1.6-fold), which may increase bleeding risk **Warfarin** INR dependent dose adjustment under expert advice and review
CrCl <15 ml/min	No anticoagulant use recommended in general use, take expert advice

SCr (μmol/L)	Women ≥60 kg* eCrCl (ml/min) (NB do not use table if weight <60 kg – see below)													Men ≥70 kg* eCrCl (ml/min) (NB do not use table if weight <70 kg – see below)												
	Age (years)													Age (years)												
	40	45	50	55	60	65	70	75	80	85	90	95	100	40	45	50	55	60	65	70	75	80	85	90	95	100
50	120	114	108	102	96	90	84	78	72	66	60	54	48	168	160	151	143	134	126	118	109	101	92	84	76	67
60	100	95	90	85	80	75	70	65	60	55	50	45	40	140	133	126	119	112	105	98	91	84	77	70	63	56
70	86	81	77	73	69	64	60	56	51	47	43	39	34	120	114	108	102	96	90	84	78	72	66	60	54	48
80	75	71	68	64	60	56	53	49	45	41	38	34	30	105	100	95	89	84	79	74	68	63	58	53	47	42
90	67	63	60	57	53	50	47	43	40	37	33	30	27	93	89	84	79	75	70	65	61	56	51	47	42	37
100	60	57	54	51	48	45	42	39	36	33	30	27	24	84	80	76	71	67	63	59	55	50	46	42	38	34
110	55	52	49	46	44	41	38	35	33	30	27	25	22	76	73	69	65	61	57	53	50	46	42	38	34	31
120	50	48	45	43	40	38	35	33	30	28	25	23	20	70	67	63	60	56	53	49	46	42	39	35	32	28
130	46	44	42	39	37	35	32	30	28	25	23	21	18	65	61	58	55	52	48	45	42	39	36	32	29	26
140	43	41	39	36	34	32	30	28	26	24	21	19	17	60	57	54	51	48	45	42	39	36	33	30	27	24
150	40	38	36	34	32	30	28	26	24	22	20	18	16	56	53	50	48	45	42	39	36	34	31	28	25	22
160	38	36	34	32	30	28	26	24	23	21	19	17	15	53	50	47	45	42	39	37	34	32	29	26	24	21
170	35	34	32	30	28	26	25	23	21	19	18	16	14	49	47	44	42	40	37	35	32	30	27	25	22	20
180	33	32	30	28	27	25	23	22	20	18	17	15	13	47	44	42	40	37	35	33	30	28	26	23	21	19
190	32	30	28	27	25	24	22	21	19	17	16	14	13	44	42	40	38	35	33	31	29	27	24	22	20	18
200	30	29	27	26	24	23	21	20	18	17	15	14	12	42	40	38	36	34	32	29	27	25	23	21	19	17

Current evidence suggests that an absolute CrCl (Cockcroft & Gault), as used in drug licence dosing studies, should be used for dosing decisions, not normalised estimated glomerular filtration rate (eGFR), especially for older patients and for narrow therapeutic index and high-risk drugs.

The tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights when eCrCl should be calculated individually (manually using the Cockcroft & Gault equation in **Box 2** or on e.g. SystmOne>clinical tools>renal calculations) *Average ideal body weight.

Based on data taken from the current Summaries of Product Characteristics (SmPCs). Available from: www.medicines.org.uk/emc/

fatal haemorrhage have been reported in Japanese elderly patients with reduced kidney function who were receiving dabigatran.[9] This resulted in the UK Medicines and Healthcare products Regulatory Agency (MHRA) issuing a reminder about appropriate use in patients with reduced kidney function (**box 1**).[9] All patients were reported to be older than 75 years, with CKD and additional risk factors for bleeding. While all received the lower dose of dabigatran (i.e. 220 mg/day) half had creatinine clearance <30 ml/min, which is a contraindication for dabigatran therapy.[9]

Rivaroxaban and apixaban are also likely to increase the risk of bleeding if used in renal impairment, and there are clear recommendations for use in the manufacturer Summary of Product Characteristics (SmPCs).[10-13] However, the SmPC is not easy for prescribers to access at time of prescribing and, although they are summarised in the *British National Formulary* (BNF),[14] the recommendations are difficult to interpret.

Renal function estimation for drug dosing

An estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation is now nationally reported when serum creatinine is monitored, following the introduction of CKD guidelines.[15,16] eGFR allows staging of renal function to guide monitoring and treatment of CKD, but it was not designed for drug dosing decisions. Historically, the Cockcroft & Gault equation[17] (CG) has been used for estimating kidney function for drug use and dosing decisions (**box 2**).

The BNF[14] now quotes renal function recommendations as 'eGFR', but the figures are those from the SmPCs, which are estimated creatinine clearance (eCrCl). They state that for most patients eGFR is an adequate estimate, but that calculation with the Cockcroft & Gault equation (eCrCl-CG) should be used for low therapeutic index and high-risk drugs. The Scottish Intercollegiate Guidelines Network (SIGN) guideline[18] states that alterations in drug dosing should be made on the basis of eCrCl-CG, as virtually all published recommendations for dose adjustment in patients with reduced kidney function, including the BNF and SmPCs are based on creatinine clearance estimated using CG.

The results of several retrospective studies suggest that use of the MDRD equation for drug dosing often yields higher doses than does the CG equation; the most conservative kidney function estimate should be used with narrow therapeutic window drugs and in high-risk subgroups, such as the elderly.[19-21] In a large (n=46,942), retrospective study comparing use of the CG and MDRD equations, major bleeding events were more frequent in individuals who received an excess dose of glycoprotein IIb/IIIa inhibitors as assessed by the MDRD equation versus CG: 21.8% *vs.* 17.8%; odds ratios MDRD 1.57 (95% confidence interval [CI] 1.35–1.84), CG 1.31 (95%CI 1.12–1.54).[22] A study using gentamicin blood levels found that MDRD overestimated renal function as age increased (29% and up to 69%) and CG underestimated renal function, though this was of a smaller magnitude (10%). CG was consistent across age and so better suited for dose calculation, especially in the elderly; age significantly influenced MDRD overestimation (p=0.037).[23]

Serum creatinine is derived from muscle turnover, and so, the weight element of the equation should be an indication of muscle mass, not excess fat; Cockcroft and Gault originally recommended using ideal or lean body weight in patients with pronounced obesity or volume overload,[17] and the BNF also states that the weight component of the equation should be ideal body weight.[14] This is particularly important when assessing kidney function for dosing decisions in overweight patients.

Decision support for oral anticoagulant dosing in reduced kidney function

The 'dosing in reduced kidney function chart' (**figure 1**) was developed to provide a visual aid on the effect of kidney function, as well as a resource to give an indication of drug choice and dosing decisions based on eCrCl.

Box 2. The Cockcroft & Gault equation[17]

$$\text{Creatinine clearance} = \frac{(140 - \text{age [years]}) \times \text{ideal body weight or actual if less (kg)} \times 1.2 \text{ for males}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Box 3. A case example of oral anticoagulant choice in AF and reduced kidney function

Mrs Flutter has been diagnosed with atrial fibrillation and has agreed to anticoagulation:

Age = 78 years

Weight = 65 kg

Serum creatinine = 90 μmol/L

Medical history: essential hypertension, stroke

eGFR 56 ml/min/1.73m^2 i.e. green area of the Renal Dosing Chart

eCrCl-CG 40–43 ml/min i.e. yellow area of the Renal Dosing Chart

So drug choice would be:

- warfarin – dose INR dependent
- or apixaban 5 mg twice daily
- or dabigatran 110 mg twice daily (HAS-BLED = 3 as female, has hypertension and past history of stroke, suggesting increased risk of bleed)
- or rivaroxaban 15 mg once daily

If eGFR had been used then it would suggest no dose adjustment would be needed.

Note: If Mrs Flutter had been 43 kg, eCrCl would need to have been calculated:

$\frac{(140\text{-}78) \times 43}{90}$ = 29.6 ml/min so in the orange area for drug choice and dosing

If 65 kg but serum creatinine = 135 μmol/L then eCrCl = 29.9 ml/min and in the orange area

Key: AF = atrial fibrillation; CG = Cockcroft & Gault equation; eCrCL = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; INR = International normalised ratio

It uses an average ideal bodyweight of 60 kg for females and 70 kg for males to give an indication of eCrCl. It should not be used for patients in acute kidney injury, who are dehydrated, or if they are under the stated weights; eCrCl-CG should then be calculated individually (manually or on electronically available calculators or decision-support systems, such as SystmOne>clinical tools>renal calculations). Patients with high muscle mass would need actual weight to be used.

To assess the individual risk of major bleeding in patients with AF, the HAS-BLED score has been suggested.[24]

Box 3 provides a worked case example showing that using eGFR would not have suggested a dose change if an NOAC was to be prescribed, and the patient could have been at a higher risk of harm.

The 'dosing in reduced kidney function chart' shown in **figure 1** has been included in primary care guidelines in Bradford, Bury, Manchester and Buckinghamshire with positive initial feedback. It has been included as part of local guidelines for use of NOACs and in AF guidelines issued to GPs; it is also being used as a quick reference guide for use in anticoagulant clinics instead of having to calculate CrCl every time when considering NOACs as alternatives to warfarin. User testing, application to other drugs, and use for education, are underway, and development of more targeted computer-decision support is planned.

Information is accurate at time of publication; manufacturer recommendations may change so there may be a need to check the SmPC.

Summary

Clearance from the body of the new oral anticoagulants is dependent on kidney function and, to reduce risk of bleeds, the level of renal function should be assessed using estimated creatinine clearance. A 'dosing in reduced kidney function chart' has been developed to aid prescribers in drug choice and dosing decisions

Conflict of interest

SW has received an honorarium from Bayer; DP has received an honorarium for advice provided to Boehringer Ingelheim; MF has received honoraria and travel assistance from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, INRStar, Medtronic, Pfizer, Roche, Sanofi-Aventis; AL has received honoraria from AM Pharma, Abbott and Baxter, and an educational grant from B Braun.

Key messages

- The clearance of the new oral anticoagulants from the body is dependent on kidney function
- To reduce risk of bleeding, the level of kidney function should be assessed using estimated creatinine clearance
- A 'dosing in reduced kidney function chart' has been developed to aid prescribers in drug choice and dosing decisions

References

1. Heidbuchel H, Verhamme P, Alings M *et al*. EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013 (doi.org/10.1093/eurheartj/eht134)

2. National Institute for Health and Clinical Excellence. The managment of atrial fibrillation. Clinical Guideline 36. London: NICE, 2006. http://guidance.nice.org.uk/CG36

3. National Institute for Health and Clinical Excellence. TA249. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. London: NICE, 2012. http://guidance.nice.org.uk/TA249

4. National Institute for Health and Clinical Excellence. TA256. Atrial fibrillation (stroke prevention) – rivaroxaban. London: NICE, 2012. http://guidance.nice.org.uk/TA256

5. National Institute for Health and Clinical Excellence. Stroke and systemic embolism (prevention, non-valvular atrial fibrillation) – apixaban. ID500 in progress. http://guidance.nice.org.uk/TA/Wave27/9

6. Connolly SJ, Ezekowitz MD, Yusuf S *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51. http://dx.doi.org/10.1056/NEJMoa0905561

7. Patel MR, Mahaffey KW, Garg J *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91. http://dx.doi.org/10.1056/NEJMoa1009638

8. Granger CB, Alexander JH, McMurray JJV *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92. http://dx.doi.org/10.1056/NEJMoa1107039

9. Medicines and Healthcare products Regulatory Agency. Dabigatran (Pradaxa): risk of serious haemorrhage – need for renal function testing. *Drug Safety Update* 2011;**5**(5). http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771

10. eMedicines Compendium UK. Summary of Product Characteristics – warfarin. http://www.medicines.org.uk/EMC/medicine/25626/SPC/Warfarin+0.5mg+Tablets/ [accessed 18/04/2013].

11. eMedicines Compendium UK. Summary of Product Characteristics – dabigatran. http://www.medicines.org.uk/EMC/medicine/24839/SPC/Pradaxa+150+mg+hard+capsules/ [accessed 18/04/2013].

12. eMedicines Compendium UK. Summary of Product Characteristics – rivaroxaban. http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/ [accessed 18/04/2013].

13. eMedicines Compendium UK. Summary of Product Characteristics – apixaban. http://www.medicines.org.uk/EMC/medicine/27220/SPC/Eliquis+5+mg+film-coated+tablets/ [accessed 18/04/2013].

14. BMJ Group and Royal Pharmaceutical Society. *British national formulary*. Volume 64. London: BMJ Group and Pharmaceutical Press, September 2012.

15. The National Collaborating Centre for Chronic Conditions. Chronic kidney disease. National clinical guideline for early identification and management in adults in primary and secondary care. NICE clinical guideline 73. London: Royal College of Physicians, 2008. http://www.nice.org.uk/nicemedia/live/12069/42116/42116.pdf

16. Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association. Chronic kidney disease in adults: UK guidelines for identification, management and referral. London: Royal College of Physicians of London, 2005. http://www.renal.org/CKDguide/full/UKCKDfull.pdf

17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.

18. Scottish Intercollegiate Guidelines Network. SIGN guideline 103. Diagnosis and management of chronic kidney disease – a national clinical guideline. Edinburgh: SIGN, 2008. http://www.sign.ac.uk/pdf/sign103.pdf

19. Nyman HA, Dowling TC, Hudson JQ *et al*. Comparative evaluation of the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) study equation for drug dosing. An opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy* 2011;**31**:1130–44. http://dx.doi.org/10.1592/phco.31.11.1130

20. Helou R. Should we continue to use the Cockcroft-Gault formula? *Nephron Clin Pract* 2010;**116**:c172–c186. http://dx.doi.org/10.1159/000317197

21. Spruill W, Wade W, Cobb H. Comparison of estimated glomerular filtration rate with estimated creatinine clearance in the dosing of drugs requiring adjustments in elderly patients with declining renal function. *Am J Geriatr Pharmacother* 2008;**6**:153–60.

22. Melloni C, Peterson ED, Chen AY *et al*. Cockcroft-Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2008;**51**:991–6. http://dx.doi.org/10.1016/j.jacc.2007.11.045

23. Roberts GW, Ibsen PM, Schioler CT. Modified diet in renal disease method overestimates renal function in selected elderly patients. *Age Ageing* 2009;**38**:698–703.

24. Pisters R, Lane DA, Nieuwlaat R *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleed in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–1100. http://dx.doi.org/10.1378/chest.10-0134