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Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study

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ABSTRACT

Objective: In clinical trials of dabigatran and rivaroxaban for stroke prevention in atrial fibrillation (AF), drug eligibility and dosing were determined using the Cockcroft-Gault equation to estimate creatine clearance as a measure of renal function. This cross-sectional study aimed to compare whether using estimated glomerular filtration rate (eGFR) by the widely available and widely used Modified Diet in Renal Disease (MDRD) equation would alter prescribing or dosing of the renally excreted new oral anticoagulants.

Participants: Of 4712 patients with known AF within a general practitioner-registered population of 930 079 in east London, data were available enabling renal function to be calculated by both Cockcroft-Gault and MDRD methods in 4120 (87.4%).

Results: Of 4120 patients, 2706 were <80 years and 1414 were ≥80 years of age. Among those ≥80 years, 14.9% were ineligible for dabigatran according to Cockcroft-Gault equation but would have been judged eligible applying MDRD method. For those <80 years, 0.8% would have been incorrectly judged eligible for dabigatran and 5.3% would have received too high a dose. For rivaroxaban, 0.3% would have been incorrectly judged eligible for treatment and 13.5% would have received too high a dose.

Conclusions: Were the MDRD-derived eGFR to be used instead of Cockcroft-Gault in prescribing these new agents, many elderly patients with AF would either incorrectly become eligible for them or would receive too high a dose. Safety has not been established using the MDRD equation, a concern since the risk of major bleeding would be increased in patients with unsuspected renal impairment. Given the potentially widespread use of these agents, particularly in primary care, regulatory authorities and drug companies should alert UK doctors of the need to use the Cockcroft-Gault formula to calculate eligibility for and dosing of the new oral anticoagulants in elderly patients with AF and not rely on the MDRD-derived eGFR.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a large community-based, cross-sectional study of over 4000 patients with atrial fibrillation (AF), in almost 90% of whom renal function could be estimated by both the Cockcroft-Gault method used in the clinical trials of the new oral anticoagulants and the Modified Diet in Renal Disease-derived estimated glomerular filtration rate used in routine clinical practice.
- The study describes the potential rather than observed risks of major bleeding resulting from inadvertent overprescribing of the new oral anticoagulants to elderly patients with AF and unsuspected renal impairment.

INTRODUCTION

Dabigatran and rivaroxaban are the first new oral anticoagulants to be licensed by the European Medicines Agency for the prevention of stroke in patients with atrial fibrillation (AF). Both agents have recently been approved by the National Institute for Health and Clinical Excellence and the Scottish Medicines Consortium.[1–4] This follows the publication of large multicentre randomised clinical trials demonstrating superiority compared with warfarin in stroke prevention with dabigatran 150 mg twice daily, and non-inferiority compared with warfarin with lower dose dabigatran (110 mg twice daily) and rivaroxaban.[5 6] Anticoagulation is now recommended for the vast majority of patients with AF and preference is given to the new agents as used in the trials over warfarin in the most recent European Society of Cardiology guidelines.[7]

Both dabigatran and rivaroxaban are excreted by the kidneys: in the case of dabigatran renal clearance is 80%[8] and with rivaroxaban it is approximately 30% as the active molecule.[9] Drug accumulation potentiating anticoagulant effects occurs with declining renal function. This is of clinical relevance, given that the population at risk with AF tends to be older, often with associated vascular risk factors that cluster with renal

impairment. Assessing creatinine clearance (CrCl) formally through isotope testing is impractical in this cohort, and estimated glomerular filtration rate (eGFR) is now widely used as a surrogate measure of renal function in both primary and secondary care. The eGFR is calculated using the Modified Diet in Renal Disease (MDRD) equation and is based on serum creatine, age, gender and ethnicity.[10] An alternative estimate of renal function (the estimated creatinine clearance (eCrCl)) is based on the Cockcroft-Gault equation which requires the inclusion of weight in addition to serum creatinine, age and gender.[10] The difference is important as serum creatinine is a less reliable predictor of CrCl at extremes of body mass (creatine synthesis is dependent on muscle bulk). In clinical trials of the new oral anticoagulants in stroke prevention in AF renal function was estimated by the Cockcroft-Gault equation and patients with eCrCl values <30 mL/min were excluded.[5 6]

The Summary of Product Characteristics (SPC) for dabigatran[11] recommends that this agent is contraindicated in patients with a CrCl <30 mL/min. Patients at increased risk of haemorrhage (patients with a CrCl of 30–50 mL/min are listed as one such group) should be individually considered for lower dose dabigatran therapy (110 mg twice daily) and this reduced dose is recommended for all patients of ≥80 years with a CrCl ≥30 mL/min. According to its SPC,[9] rivaroxaban is contraindicated in patients with a CrCl of <15 mL/min and the dose should be reduced from 20 to 15 mg daily in those with a CrCl of 15–49 mL/min. In each SPC the recommended method for estimation of renal function as CrCl is Cockcroft-Gault. Introduction of dabigatran into clinical practice in other countries has been associated with several reports of major haemorrhage, particularly in elderly patients with impaired renal function,[12] and the Medicines and Healthcare products Regulatory Agency (MHRA) has recently issued two sets of advice with regard to bleeding risks.[13 14] It recommends that renal function be checked before starting dabigatran and that it should be reassessed at least annually in patients >75 years or with renal impairment or if a decline in renal function is suspected during treatment. However, although referring to CrCl, the method of assessment of renal function is not stated. In the UK, all biochemistry laboratories provide an MDRD-derived eGFR (mL/min/1.73 m^2) in keeping with national guidance.[15] Many clinicians will use this result to estimate renal function at initiation or follow-up of the new oral anticoagulants.

This study aimed to compare the two methods of assessment of renal function to determine whether substitution of Cockcroft-Gault by MDRD would affect either the selection of patients for the new oral anticoagulants or the dose of dabigatran or rivaroxaban these patients were prescribed. This is important to establish because the bleeding risk of warfarin is increased in patients with renal impairment[16] and the bleeding risks of the new agents might be even higher since, unlike warfarin, they are excreted through the kidneys and therefore accumulate with renal dysfunction. Moreover, and again unlike warfarin, they lack an antidote in the event of bleeding.

METHODS

The study was set in the three geographically contiguous east London primary care trusts (PCTs) of Newham, Tower Hamlets and City and Hackney, with a combined general practitioner (GP)-registered population of 930 079 in April 2012. The populations of these PCTs come from among the eight most socially deprived localities in Britain, with more than 50% of the population being of non-white ethnic origin. In June 2012, demographic and clinical data were obtained from 137/141 general practices in east London covering more than 98% of the GP-registered population in the three PCTs. All data were anonymous and managed according to the UK NHS information governance requirements.

Clinical and demographic data collection

Practice computer databases were interrogated using Egton Medical Information Systems Web software. All adult patients (18 years and over) with a Read code for AF were included in the study.

Demographic variables extracted included age, gender and ethnicity. Ethnicity was self-reported by patients and collapsed into five categories: white (British, Irish, other white); south Asian (Bangladeshi, Indian, Pakistani, other Asian, white and Asian); black (African, Caribbean, white and Caribbean, white and African); other (Chinese, other mixed, and any other recorded ethnic group) and not stated.

Clinical variables included weight and the latest serum creatinine value (in µmol/L) within the past 2 years. Different methods for measuring the serum creatine are used in the study area; however, as we report elsewhere,[17] differences between laboratory techniques result in negligible variations in estimates of renal function which we do not consider will affect its overall classification.

Renal function

For each patient in the study, renal function was calculated using both the Cockcroft-Gault and the MDRD methods. Ethnicity recording was available for the entire cohort and the black ethnicity correction factor was added to the MDRD formula prior to analysis.

eGFR using MDRD=$186\times(\text{creatine}/88.4)^{-1.154}\times\text{age}^{-0.203}\times(0.742 \text{ if female})\times(1.21 \text{ if black})$. The result is expressed in mL/min/1.73 m^2.

eCrCl using Cockcroft-Gault=$(140-\text{age})\times\text{weight in kg}\times1.23$ ($\times0.85$ if female)$\times$creatine. The result is expressed in mL/min.

Statistical analysis

All statistical analyses were performed using Stata V.12 (StataCorp LP). Concordance between the two methods

of measurement was examined using Bland-Altman plots. Each result was entered into one of several categories of renal function that would be used for selection for or dosing of dabigatran or rivaroxaban except that a category of eCrCl of ≥70 mL/min was also included to assess whether any patient with relatively normal renal function would be differently classified so as to affect selection or dosing. The proportions of cases in each category of CrCl estimated by Cockcroft-Gault equation which would be misattributed, were the MDRD equation to be used, were calculated.

Logistic regression was used to examine the odds of the MDRD-based categorisation of eGFR being different to CrCl estimated by the Cockcroft-Gault method, so as to affect selection for or dosing of dabigatran or rivaroxaban, according to age, sex, weight and clustering by general practice.

RESULTS

A total of 4712 patients with AF were identified. Their demographic features by gender, ethnicity and age are shown in table 1. Of these, 419 had missing serum creatine values, one had a serum creatine value below 30 µmol/L, 268 had a missing value for weight and 96 individuals were missing both creatinine and weight, leaving 4120 (87.4%) patients with sufficient data to allow calculation of renal function by both Cockcroft-Gault and MDRD methods.

A Bland-Altman plot (figure 1) demonstrates that, relative to Cockcroft-Gault, MDRD slightly underestimates renal function at higher levels and tends to overestimate at lower levels.

To assess the impact of the method used for estimation of renal function on potential dosing of the new anticoagulants, patients were categorised by renal function as estimated by Cockcroft-Gault equation and the proportions given would change categories if estimated by MDRD are given in tables 2 and 3. The results are shown for the entire cohort for rivaroxaban and separately for those <80 and ≥80 years for dabigatran since age affects the dosing of the latter.

Dosing dabigatran

Dabigatran is contraindicated if the eCrCl is <30 mL/min and its dosage should be reduced (from 150 to 110 mg twice daily) in those ≥80 years. For those <80 years, dose reduction should be considered on an individual basis in those with a Cockcroft-Gault eCrCl of 30–50 mL/min, particularly if there is an additional bleeding risk. Table 2 shows that of the 1414 patients with AF 80 years of age or older, 211 (14.9%) were ineligible for dabigatran because of an eCrCl <30 mL/min according to Cockcroft-Gault, but would have been judged eligible for dabigatran as they had an eGFR ≥30 mL/min/1.73 m^2 by MDRD. The proportion of patients being misclassified in the opposite direction (ie, being judged ineligible for treatment due to their MDRD eGFR) was much smaller at 0.9%. For the 2706 patients younger than 80 years there was a small proportion of misclassification in either direction with around 1% being incorrectly judged eligible and 10% potentially receiving too high or too low a dose.

Table 1 Summary of demographic and clinical features of patients with atrial fibrillation (AF; N=4712)

Demographic variables	Patients with AF	Percentage of total population
PCT		
City and Hackney	1670	36
Newham	1644	35
Tower hamlets	1398	30
Sex		
Female	2122	44
Male	2590	56
Ethnic group		
White	3450	73
South Asian	481	10
Black	491	11
Other	209	4
Not stated/refused	62	1
Missing	119	2
Age (years)		
18–35	62	2
35–44	132	3
45–54	360	8
55–64	684	15
65–74	1092	23
75–84	1495	32
85+	887	19
Weight (kg)		
<60	689	15
≥60	3755	80
Weight missing	268	6
Clinical variables recorded		
Weight	4444	94
Creatinine	4292	91

PCT, primary care trust.

Dosing rivaroxaban

Rivaroxaban should be dose reduced to 15 mg daily (from 20 mg daily) if the Cockcroft-Gault eCrCl is 15–49 mL/min and is contraindicated if it is <15 mL/min. Table 3 shows that of the 4120 patients with AF, 11 (0.3%) were ineligible for rivaroxaban because of an eCrCl <15 mL/min according to Cockcroft-Gault, but would have been judged eligible for rivaroxaban as they had an eGFR ≥15 mL/min/1.73 m^2 by MDRD. A further 556 patients (13.5%) would be judged to require a reduced dose of rivaroxaban because of an eCrCl between 15 and <50 mL/min according to Cockcroft-Gault, but no reduction in dose would have appeared necessary as they had an eGFR ≥50 mL/min/1.73 m^2 by MDRD. The proportions of patients being misclassified in the opposite direction (ie, either being judged ineligible for treatment or

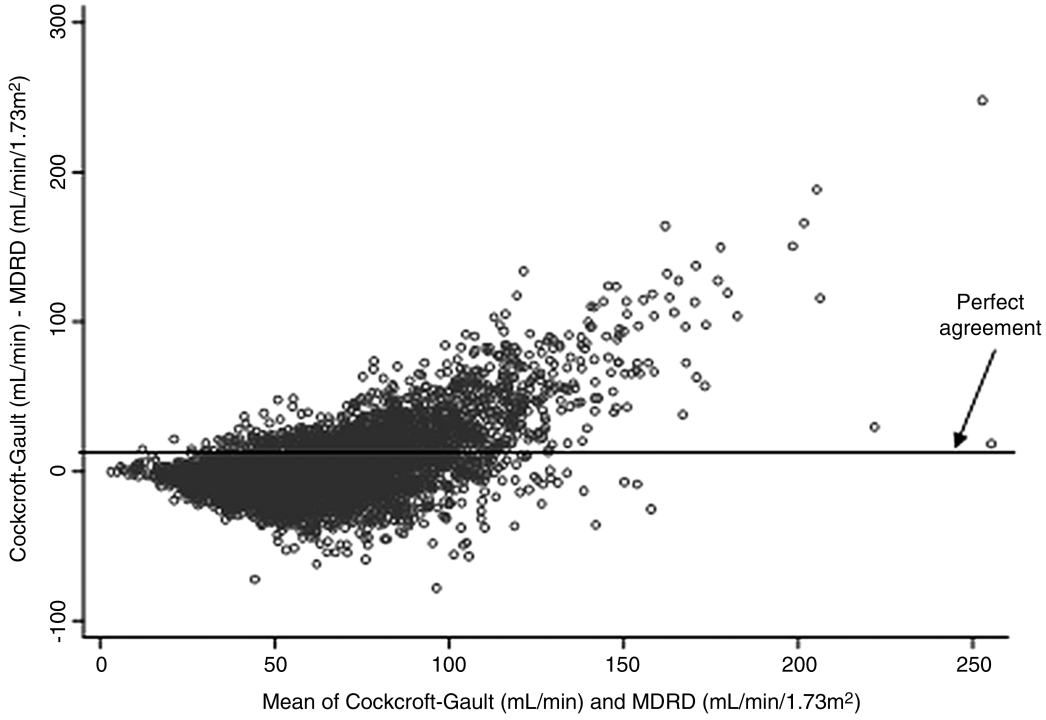

Figure 1 Agreement between Cockcroft-Gault and Modified Diet in Renal Disease estimation (N=4120).

requiring a reduced dose due to their MDRD eGFR) were smaller at 0.1% and 4.5%, respectively.

Effect of other variables on differences between eCrCl and eGFR

As shown in the regression analysis in table 4, those aged ≥80 years were more than 15-fold (OR=15.41; 95% CI 10.00 to 23.75) more likely to be incorrectly judged eligible for dabigatran by MDRD (as Cockcroft-Gault judged them ineligible). Those whose weight was <60 kg were eightfold (OR=8.22; 95% CI 6.05 to 11.18) more likely to be incorrectly judged eligible for dabigatran and a significant but smaller effect was also seen in women (OR=1.45; 95% CI 1.05 to 2.00). For rivaroxaban, patients ≥80 years had almost 10 times (OR=9.71; 95% CI 1.06 to 88.5) the odds of being incorrectly judged eligible by MDRD. Those whose weight was <60 kg were more than 12-fold (OR 12.73; 95% CI 1.85 to 87.53) more likely to be incorrectly judged eligible for rivaroxaban. The age effect (ie, ≥80 years) on renal function assessment was evident even in patients with MDRD-derived eGFR values ≥70 mL/min/1.73 m^2: of 311 such patients 27% had a Cockcroft-Gault eCrCl of <50 mL/min (data not shown).

DISCUSSION

Our analysis of more than 4000 patients with AF in primary care shows that there would be clinically important potential risks to prescribing practice for the first

Table 2 Treatment decisions made about dabigatran using the eGFR from the MDRD method assuming the eCrCl from the Cockcroft-Gault (CG) method is the gold standard

Treatment recommendations for dabigatran	Measured values by CG and MDRD methods	Patients <80 years of age		Patients ≥80 years of age	
		N	Per cent	N	Per cent
Undertreated—contraindication incorrectly identified by MDRD	CG ≥30 and MDRD <30	41	1.5	13	0.9
Underdosed—dose reduction incorrectly identified by MDRD	CG ≥50 and MDRD 30–<50	149	5.5	–	–
Correctly treated		2351	86.9	1190	84.1
Overdosed—recommendation for dose reduction missed by MDRD	CG 30–<50 and MDRD ≥50	144	5.3	–	–
Overtreated—contraindication missed by MDRD	CG <30 and MDRD ≥30	21	0.8	211	14.9
All patients		2706	100.0	1414	100.0

eCrCl, estimated creatine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modified Diet in Renal Disease.

Table 3 Treatment decisions made about rivaroxaban using the eGFR from the MDRD method assuming the eCrCl from the Cockcroft-Gault (CG) method is the gold standard

Treatment recommendations for rivaroxaban	Measured values by CG and MDRD methods	All patients N	All patients Per cent
Undertreated—contraindication incorrectly identified by MDRD	CG ≥15 and MDRD <15	5	0.1
Underdosed—dose reduction incorrectly identified by MDRD	CG ≥50 and MDRD 15–<50	183	4.4
Correctly treated		3365	81.7
Overdosed—recommendation for dose reduction missed by MDRD	CG 15–<50 and MDRD ≥50	556	13.5
Overtreated—contraindication missed by MDRD	CG <15 and MDRD ≥15	11	0.3
All patients		4120	100.0

eCrCl, estimated creatine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modified Diet in Renal Disease.

two new oral anticoagulants licensed in the UK for the prevention of stroke if the widely available MDRD eGFR formula were used instead of Cockcroft-Gault to estimate CrCl, especially in patients aged 80 years and over. These patients are a very important group for whom there are major attractions for the new oral anticoagulants because of their ease of use as well as their efficacy and safety evident in clinical trials. AF is both particularly prevalent and an important cause of stroke in this patient group but they are also more susceptible to the bleeding complications of anticoagulant therapy.[18] Of the patients who are 80 years and over, in whom the bleeding risk appears highest, 15% would be incorrectly judged eligible for dabigatran based on the MDRD rather than the Cockcroft-Gault formula. Similar findings were reported from a recent Swedish study examining surrogates of renal function and drug dosing.[19] A proportion of patients would receive too high a dose of rivaroxaban had the MDRD formula been used. This suggests that the Cockcroft-Gault formula should be used for all patients who are 80 years or more (69% of whom had an eCrCl <50 mL/min compared with 15.9% of those under 80 years) although in clinical practice it would be simpler and safer to adopt this approach for all patients regardless of age. This may be particularly the case since a second factor, being underweight (<60 kg), also independently increased the chance of incorrectly being judged eligible for these agents.

The absolute risk of major bleeding on warfarin in recent registries[20] and contemporary trials[5 6] is about 1–3% per year and might therefore increase to approximately 4% annually in those with renal impairment.[16] The risks and benefits of warfarin are not always clear in this setting in which the stroke risk is also increased.[21 22] Although the safety of both dabigatran and rivaroxaban appears satisfactory down to a CrCl of 30 mL/min[5 23] clinical data are lacking for patients with CrCl values <30 mL/min and the recommendation for dosing rivaroxaban in those with an eCrCl of 15–30 mL/min is based on pharmacokinetic modelling. In a meta-analysis of the impact of impaired renal function on bleeding in patients receiving another form of anticoagulation that is renally excreted—the low-molecular-weight heparin, enoxaparin—therapeutic doses were associated with an almost fourfold increase in major bleeding risk in those with a CrCl of 30 mL/min or less compared with those with a CrCl >30 mL/min.[24] From our data and depending on the precise impact of dabigatran, we estimate that of 1000 patients of 80 years or more with AF who might be treated with this agent, approximately 150 with an eCrCl <30 mL/min would be inappropriately treated (because eGFR ≥30 mL/min/1.73 m^2) and about 20 might develop major bleeding annually as a result. Many clinicians will use their judgement and prescribe or dose on the side of caution at thresholds of eGFR (eg, at or around 30 mL/min/1.73 m^2). We believe that using the

Table 4 OR for likelihood of being over treated due to a contraindication being missed by MDRD adjusted for age, sex and weight (all variables adjusted for one another)

Variable	Dabigatran OR (95% CI)	Dabigatran p Value	Rivaroxaban OR (95% CI)	Rivaroxaban p Value
Male (ref)	1		1	
Female	1.45 (1.05 to 2.00)	0.024	1.65 (0.26 to 10.45)	0.593
Age (years)				
<80	1		1	
≥80	15.41 (10.00 to 23.75)	<0.001	9.71 (1.06 to 88.5)	0.044
Weight (kg)				
≥60	1		1	
<60	8.22 (6.05 to 11.18)	<0.001	12.73 (1.85 to 87.53)	0.01

MDRD, Modified Diet in Renal Disease.

Cockcroft-Gault equation in at-risk groups would better allow both appropriate dosing (avoiding under-dosing) and minimise overanticoagulation.

The four-variable MDRD eGFR is provided alongside serum creatinine for all laboratory analyses within the UK and is the basis of much prescribing in primary and secondary care. The British National Formulary (BNF; September 2012)[25] recommends use of eGFR for dosing of dabigatran and rivaroxaban in AF. In October 2012, the electronic BNF entry for dabigatran was altered to include the manufacturer's recommendation that the Cockcroft-Gault method should be used to calculate CrCl. Our analysis reinforces the need for clinicians to use the Cockcroft-Gault equation when prescribing these agents.

The selection of the method to estimate renal function in prescribing medications that are excreted by the kidneys is not new to controversy—the equations are intended for the identification of chronic kidney disease (CKD) rather than as tools for pharmacokinetic modelling, and their accuracy and utility are questionable in those with a true GFR of >60 mL/min/1.73 m^2. Serum creatinine varies depending on the assay used, diet, muscle mass and body size. Equations are only useful when kidney function is stable, and drugs with a narrow therapeutic index are often better dosed on more formal assessment of function in those who appear to have CKD. Trials of the new oral anticoagulants have used the Cockcroft-Gault equation to calculate CrCl,[5 6] as it is practical and has been widely used for this purpose in the past. The more widely available and better-performing MDRD formula and a newer CKD-EPI formula have both been tested as tools for dosing drugs.[10 26] A number of studies have reported the MDRD equation as leading to higher doses being used when compared with Cockcroft-Gault,[27] a finding consistent with our own. We advocate caution over potential adverse effects related to inappropriate dosing when using MDRD compared with Cockcroft-Gault. Each equation is recognised to either overstate (MDRD) or understate (Cockcroft-Gault) renal function compared with formal measurement in those >65 years (a key constituency for oral anticoagulant use). Both equations are uncorrected for body surface area in those at the extremes of body weight. It is worth emphasising that the creatinine assay used and the population studied may in itself lead to variation—east London's multiethnic (>50% non-white ethnic origin) population is not typical of the UK as a whole.

The convenience and efficacy of the new anticoagulants mean that they may be considered for many of the estimated 1 million people with AF in the UK (based on a 1.5–2% prevalence in the general population)[18] who are thought to require anticoagulation, only approximately 50% of whom are currently prescribed warfarin.[28–30] Our findings, therefore, may apply to a large number of patients and are particularly relevant to the elderly (≥80 years), all of whom should be considered for treatment with oral anticoagulants in the absence of a contraindication and with one of the new agents in broad preference to warfarin according to recent European Society of Cardiology guidelines.[7] Although different methods of measurement of renal function appear to be predictive of bleeding risk in elderly patients on warfarin,[31] until evidence is provided that it is safe to use the MDRD formula rather than Cockcroft-Gault, it is important that clinicians and pharmacists are aware that use of the eGFR may expose patients to increased risks of bleeding. This is particularly pertinent to primary care because GPs will increasingly take responsibility for selection of the new oral anticoagulants with eligibility and dose adjustment according to measurement of renal function. Although in hospital practice there is familiarity with using the Cockcroft-Gault method of calculation of CrCl, for example, for dosing of aminoglycosides, this is not the case for drugs that are used in primary care. This issue requires further clarification by the MHRA. Drug companies too should alert clinicians to the importance of using the Cockcroft-Gault method of calculation of CrCl for all patients being considered for or receiving dabigatran or rivaroxaban for stroke prevention in AF.

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