BMJ open

Dangerously higher recommended doses of dabigatran in the elderly, particularly in women, with the use of the MDRD4 formula to estimate glomerular filtration rate: A data simulation study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002686
Article Type:	Research
Date Submitted by the Author:	05-Feb-2013
Complete List of Authors:	Helldén, Anders; Division of Clinical Pharmacology, Department of Laboratory Medicine Odar-Cederlöf, Ingegerd; Division of Clinical Pharmacology, Department of Laboratory Medicine Nilsson, Goran; Center for Clinical Research, Sjöviker, Susanne; Department of Drug Management and Informatics, Centre for Health Care Improvement, Stockholm County Council Söderström, Anders; Farsta home care center at the time of the study, von Euler, Mia; Division of Clinical Pharmacology, Department of Laboratory Medicine at the time of the study Öhlén, Gunnar; Quality and Patient Safety, Karolinska University Hospital Bergman, Ulf; Division of Clinical Pharmacology, of Laboratory Medicine
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Cardiovascular medicine, Neurology, Pharmacology and therapeutics, Renal medicine
Keywords:	Thromboembolism < CARDIOLOGY, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, Anticoagulation < HAEMATOLOGY, Adult nephrology < NEPHROLOGY, Stroke < NEUROLOGY

ARTICLE SUMMARY

Article focus

- The thrombin inhibitor dabigatran is eliminated by renal excretion. Severe bleeding, even fatal, was reported, mainly in elderly patients with impaired renal function.
- Dosing should be adjusted according to renal function, i.e. by the Cockcroft-Gault equation. However, in many countries the (eGFR) abbreviated Modification of Diet in Renal disease (MDRD4) equation is used in clinical practice for estimation of renal function.
- We studied whether use of MDRD4 would show different estimates and thus different recommended doses for dabigatran and for two other renally excreted drugs, gabapentin, and valaciclovir, in a group of elderly patients.

Key messages

- A significantly larger group of elderly subjects would receive a higher dose of the three drugs if MDRD4 was used for determination of dose. This may be one explanation of the cases of serious haemorrhage reported for dabigatran and CNS side effects for gabapentin and valaciclovir.
- A method to optimize ongoing therapy is to determine plasma concentrations of the drug – (TDM- Therapeutic Drug Monitoring).

Strengths and limitations of this study

- The main strength of this study is the number of elderly subjects and the different settings from where they were recruited, reflecting a mean of the older Swedish population.
- Limitations are that this is a data simulation study and no dabigatran, gabapentin, or valaciclovir dose has been given to the subjects.

- In addition, we have not performed any gold standard methods, such as iohexol clearance, to elucidate the true GFR in the studied subjects.

INTRODUCTION

The oral thrombin inhibitor dabigatran etexilate (Pradaxa®) is marketed as an alternative to warfarin for prevention of venous thromboembolism (VTE) in atrial fibrillation (AF). Dabigatran etexilate is a prodrug metabolized to the active species dabigatran, which is eliminated primarily by the kidneys. Renal function is therefore an important factor for its clearance rate.[1, 2]

Serious cases of hemorrhage, even fatal, have been reported with the drug,[3-5] mainly in elderly patients with severe renal impairment.[4, 6] Hemorrhage is a dose- and concentration-dependant adverse reaction, shown during the clinical trials with the drug, and the risk for hemorrhage increases in patients with low renal function.[7] To prevent this serious risk, renal function should be evaluated by estimation of creatinine clearance including age, sex, serum creatinine, and weight, based on the equation that was used during the clinical trials, presented as absolute values (mL/min) (Cockcroft-Gault- CG).[8] Later methods, such as the original Modification of Diet in Renal Disease (MDRD) equation, the abbreviated MDRD equation (MDRD4), and the Chronic Kidney Disease Epidemiology initiative (CKD-Epi) equation have been introduced providing estimates of glomerular filtration rate (eGFR) as a relative value of mL/min/1.73m^2.[9-11] In many countries, MDRD4 is used in clinical practice. Recently, FDA draft guidance for industry suggested that both CG and MDRD can be used for pharmacokinetic studies in patients with impaired renal function.[1] The latter equation uses standardized serum creatinine concentrations traceable to Isotope-Dilution Mass Spectrometry (IDMS), resulting in a lower serum creatinine concentration (compensated) compared to the old Jaffe method (uncompensated).[12-15] The MDRD formula has shown to provide significantly

higher eGFR values in the elderly, potentially increasing the risk for dabigatran-induced hemorrhages.[16-19] For the purpose of the present study we also studied two other drugs dependent on renal function; gabapentin, that is excreted unchanged by the kidneys, and valaciclovir, that forms a toxic metabolite in patients with renal impairment.[20]

SUBJECTS AND METHODS

Data from subjects 65 years and older were compiled from six different studies on renal function in the elderly. All subjects were Caucasians. One study was performed in a home care center (N=88)[21]; four studies were performed at an intermediary care unit of internal medicine within the emergency department (N=270),[18, 22-24] all in Stockholm; and finally one study of 75-year-old subjects was performed in the city of Västerås (N=432).[25] We simulated the doses of dabigatran that these subjects would be prescribed based on their renal function, i.e. 300 mg if creatinine clearance is higher than 50 mL/min; 220 mg if creatinine clearance is 30-50 mL/min and associated with high risk of bleeding; and finally contraindicated if creatinine clearance is less than 30 mL/min. The rationale behind our stratification is that exposure to dabigatran increases 3- and to 6-fold in patients with moderate and severe renal impairment.[26] Patient characteristics, such as weight, height, age, and sex were recorded. Complete data were retrieved for 790 subjects, 432 women and 358 men (Table I). Ethical approval was obtained for five studies; the sixth was a local quality assessment not requiring ethical approval in Sweden. From the six studies, only laboratory and demographic data about the included subjects were received by the investigators and all other information was blinded.

Table 1. Demographic data (age, sex, weight, length, BSA= body surface area, BMI= body mass index) for 790 individuals aged 65 and older divided between men and women in Sweden

from six different studies of the elderly. Renal function estimates with different methods: CG= Cockcroft & Gault. MDRD4= abbreviated Modification of Diet in Renal Disease equation. Divide by 88.4 to get creatinine concentration in mg/mL. Mean ± SD, P<0.05 is regarded as significant.

	All (N=790)	Female (N=432)	Male (N=358)	P-value
Age (years)	77.6 ± 5.7	78.0 ± 6.0	77.1 ± 5.2	<0.05
Weight (kg)	70.2 ± 13.9	66.0 ± 14.0	75.2 ± 12.1	< 0.001
Height (cm) (N=590)	167 ± 8.6	161.3 ± 5.5[a)]	174.0 ± 6.1[b)]	< 0.001
BSA (m^2) (N=590)	1.8 ± 0.18	1.7 ± 0.17[a)]	1.9 ± 0.14[b)]	< 0.001
BMI (N=590)	25.5 ± 4.2	25.7 ± 4.6[a)]	25.1 ± 3.5[b)]	0.073
Compensated P-creatinine (µmol/L)	102.2 ± 42.1	95.6 ± 35.0	110.1 ± 48.3	< 0.001
Uncompensated P-creatinine (µmol/L)	120.2 ± 38.8	114.0 ± 32.2	127.3 ± 44.4	< 0.001
CG uncompensated P-creatinine (mL/min)	44.2 ± 14.8	39.8 ± 13.2	49.5 ± 15.0	< 0.001
MDRD4 (mL/min/1.73m^2)	59.6 ± 20.7	55.3 ± 19.4	64.7 ± 21.0	< 0.001

[a)] N=322
[b)] N=268

Statistics

Statistical analysis was performed with Statistica (Statsoft, Tulsa). ANOVA was used to compare the difference in renal clearance in relation to age. Continuous variables are expressed as mean and standard deviation (SD).

Estimation of renal function and drug dosage

Plasma creatinine was analyzed at the laboratory of Clinical Chemistry at Karolinska University Hospital and at the laboratory of Chemistry at Västerås hospital with a modified Jaffe method, traceable to IDMS[27] and similar to an enzymatic method, i.e. "compensated" creatinine. These values have then been recalculated to "uncompensated" creatinine when used in the CG_{old} equation (uncompensated creatinine = compensated creatinine * 0.92+26) to resemble the CG results gained in the initial studies of dabigatran.[13, 28] In addition, we

investigated if similar relation could be shown with two other older drugs with renal excretion; gabapentin and valaciclovir. Compensated creatinine has been incorporated in the MDRD4 equation (Table II). We then simulated the dabigatran, gabapentin and valaciclovir dose each subject would receive based on the resulting renal clearance. Estimated GFR (eGFR) is as usual given in relative value (mL/min/1.73m^2).

Table II. Estimations of renal function used in a cohort of elderly subjects by two different equations: The Cockcroft & Gault equation with uncompensated P-creatinine (CG_{old}) and the MDRD4 equation calculated with compensated creatinine traceable to IDMS. No correction factor for afro-Americans has been included as all subjects were Caucasians. P-creatinine concentration in µmol/L.

$$CG_{old} = \frac{1.23 \times (140 - age) \times weight}{(P - creatinine \times 0.92 + 26)} (\times 0.85\ female) \text{ mL/min (absolute)}$$

$$MDRD4 = 175 \times \left(\frac{P - creatinine}{88.4}\right)^{-1.154} \times age^{-0.203} (\times 0.742\ female) \text{ mL/min/1.73m}^2 \text{ (relative)}$$

RESULTS

Renal function decreased significantly (p< 0.001) in relation to increasing age for both estimations (Figure 1). CG_{old} produced the lowest estimated renal function, 44.2 ± 14.8 mL/min, and MDRD4 the highest, 59.6 ± 20.7 mL/min/1.73 m^2 (P<0.001), absolute mean difference 13.5, 95% CI 12.9 to 14.2 (Table I). A data simulation showed a significantly higher mean dose of dabigatran with MDRD than with CG_{old}: 260 ± 76 mg compared to 208 ± 103 mg (25% higher dose) (P<0.001). The difference was even more pronounced for women, 253 ± 73 mg for MDRD4 compared to 186 ± 105 mg for CG_{old} (+36%) and less for men, 267 ± 77 mg for MDRD4 compared to 234 ± 94 mg for CG_{old}, (+14%) but still highly significant (P<0.001).

For women, the MDRD4 equation resulted in an increased dose compared to the CG_{old} in 221 subjects (51%), a lower dose in eight subjects (2%) and an unaltered dose in 203 subjects (47%). Dabigatran would be contraindicated (creatinine clearance less than 30 mL/min) in 18% of all subjects using CG_{old} and in 7% of those with the MDRD4 equation. Thirty-three per cent of all subjects would be recommended a full dose of dabigatran if CG_{old} is used, whereas the corresponding number for MDRD4 is 67% (Figure 2 a). The same pattern was shown for valaciclovir and gabapentin; mean valaciclovir dose calculated with CG_{old} was 2156 ± 699 mg compared to 2602 ± 603 mg with MDRD4 (21% higher dose) ($P<0.001$) (Figure 2 b). Gabapentin mean dose was 663 ± 266 mg when calculated with CG_{old} compared to 910 ± 406 mg with the MDRD4 (+37%) ($P<0.001$) (Figure 2 c).

DISCUSSION

Our study shows that the change from the CG equation with uncompensated P-creatinine by the Jaffe analysis method to the MDRD4 equation with a compensated creatinine traceable to IDMS, results in significantly higher renal function value in the elderly. Consequently the dose recommendation based on MDRD4 results in higher doses of dabigatran, particularly in elderly female subjects. This may have contributed to the serious and sometimes fatal adverse drug reactions (ADRs) reported around the world.[4, 6, 29, 30] We found similar results for two older renally excreted drugs (also developed during a period when uncompensated creatinine by the Jaffe creatinine method was used), valaciclovir, and gabapentin for comparison.

The problem is similar to that which would be faced when treating patients with other renally excreted drugs (including metabolites) e.g. antibiotics, pregabalin, metformin, and morphine. Other researchers have found similar results.[15-17, 31] There are reports suggesting that MDRD can be used for drug dosing,[32] whereas others have questioned it.[33-35]

In Europe, a "Dear Healthcare Professional Letter" was circulated in October 2011 to point out that renal function should be estimated in all patients before treatment with dabigatran. This recommendation was released in order to exclude those patients with creatinine clearance less than 30 ml/min, where dabigatran is contraindicated due to increased risk of bleeding.[36] Renal function should be re-estimated in clinical situations where renal function may decline and at least annually in patients older than 75 years (corresponding to 29% of all dabigatran users in Sweden). The current European dabigatran Summary of Products Characteristics (SPC) points out that in patients with advanced age and moderately impaired renal function (creatinine clearance 30 – 50 ml/min) dose reduction should be considered and the patients should be closely observed regarding bleeding or anemia.[37]

Dose recommendations in relation to renal function given in the SPCs are in general based on endogenous creatinine clearance or estimated creatinine clearance according to the CG equation (including P-creatinine, age, sex, and weight) in mL/min, an absolute value of clearance.[1] This is also the case for dabigatran.[38] Different equations have been used in the trials such as the CG equation,[39-41] the original MDRD equation,[7, 9] measured creatinine clearance, and sinistrin clearance.[26] In one study only creatinine clearance is mentioned, without stating the clearance estimation method.[41] Since then, worldwide standardisation of the creatinine method has resulted in a lower reference range for creatinine and thus higher clearance values in patients with low P-creatinine, e.g. elderly patients. Other researchers have also pointed out the differences among results from the various methods to estimate renal function and the consequential differences in doses.[15, 17, 31, 42]

The "Dear Healthcare Professional Letter" states that dose recommendations should be based on equations based on sex, age, and weight.[36] This statement excludes the MDRD4 equation and the CKD-Epi equation as they do not include weight in the calculation. With

MDRD4 (we found similar results with the CKD-Epi formula- data not shown) more patients will be recommended higher doses of dabigatran than with CG and will be exposed to greater risk of dose-concentration dependent adverse drug reactions, e.g. hemorrhage. There is no antidote to give if the dose is too high, nor in trauma or acute operations. The only treatment available presently is symptomatic or possibly dialysis.[43]

Another important factor is to use the patient's absolute renal function and not the relative clearance the patient or subject would have had if his/her body surface area would have been 1.73 m^2 since most dose recommendations based on dose-effect studies use the absolute clearance.[34] "Absolute"= without correction for body surface area (mL/min) and "relative"= with correction for body surface area (mL/min/1.73m^2). In most patients, the difference between the two may be small but in certain patients, e.g. elderly women, in particular those with a body surface area (BSA) smaller than (the standard) 1.73 m^2, the difference may be considerable. A case report from France describes two elderly dabigatran-treated women 84 and 89 years old, respectively, one with a fatal and one with a serious hemorrhage. Plasma concentrations of dabigatran were reported to be high. Both patients had low weight, low relative creatinine clearance of 29 and 32 mL/min/1.73 m^2, respectively, and probably an absolute creatinine clearance below 30 ml/min, which is a contraindication for dabigatran treatment.[4]

Elderly patients with decreased renal function are at particular risk for dose- and concentration-dependent ADRs. Their reduced renal function is not always noticed.[18] There is a great need of evidence-based support when prescribing drugs for elderly patients.[44] Before new methods to estimate renal function, e.g. MDRD4 and CKD-EPI, all being surrogate markers for renal function, are used for drug dosing in the elderly, the consequences must be well documented, including pharmacokinetic modeling and TDM (Therapeutic Drug Monitoring). In the most recent draft guideline from the US-FDA, both CG and MDRD4 may

be used.[1] The current "Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function" from EMEA 2004 states that measuring GFR should be based on accurate well established methods (such as iohexol clearance).[45] In contrast to the US-FDA, there is no practical recommendation from EMA.

We found that the method used to estimate renal function has impact on recommended dabigatran doses in the elderly. Further studies may answer the question if dabigatran dose-rate in the elderly should be adjusted for decreases in creatinine clearance according to standard pharmacological principles.[46] In addition, to prevent dangerously high doses of older remedies in the elderly, a comparison factor between older and newer assays to determine P-creatinine may be needed, however impractical.

Subsequently, one question remains to be answered: Can we rely on the measurements of renal function made in the initial dabigatran pharmacokinetic studies? This needs urgently to be elucidated. The authors suggest that drug therapy in the elderly in general is more frequently guided by TDM, if available.

CONCLUSION

This data simulation study shows that the MDRD4 equation would result in higher doses of dabigatran, gabapentin, and valaciclovir to elderly subjects, particularly in women, compared to the CG equation that was used during the clinical trials, and thus increase the risk of dose and concentration-dependent ADRs. Although dose recommendations for dabigatran in the SPC refer to both renal function and age, creatinine clearance according to CG is the basis for calculating recommended doses for dabigatran as for many other drugs with renal elimination. Doses based on other methods may be associated with considerable risk.

REFERENCES:

1. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. DRAFT GUIDANCE http://wwwfdagov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf 2010 (accessed 2012-02-03).
2. PRADAXA, EPAR. Summary for the public. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/medicines/human/medicines/000829/human_med_000981jsp&murl=menus/medicines/medicinesjsp&jsenabled=true (accessed 2012-10-28).
3. Casado Naranjo I, Portilla-Cuenca J, Jiménez Caballero P, Calle Escobar M, Romero Sevilla R. Fatal intracerebral hemorrhage associated with administration of recombinant tissue plasminogen activator in a stroke patient on treatment with dabigatran. Cerebrovasc Dis 2011;**32**:616-9. doi: 10.1159/000334578. Epub 2011 Dec 1.
4. Legrand M, Mateo J, Aribaud A et al. The use of dabigatran in elderly patients. Arch Intern Med 2011;**171**:1285-6. doi: 10.1001/archinternmed.2011.314.
5. Chen B, Viny A, Garlich F et al. Hemorrhagic complications associated with dabigatran use. Clin Toxicol 2012;**50**:854-7. doi: 10.3109/15563650.2012.721888. Epub 2012 Sep 12.
6. Food and Drug Administration. www.fda.gov/Drugs/DrugSafety/ucm282724.htm (accessed 12-02-03).
7. Ezekowitz MD, Reilly PA, Nehmiz G et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;**100**:1419-26. Epub 2007 Aug 17.

8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;**16**:31-41.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;**130**:461-70.
10. Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;**145**:247-54.
11. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;**150**:604-12.
12. Wuyts B, Bernard D, Van den Noortgate N et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. Clin Chem 2003;**49**:1011-4.
13. Chan MH, Ng KF, Szeto CC et al. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2004;**41**:482-4.
14. Delanghe J, Speeckaert M. Creatinine determination according to Jaffe- what does it stand for? NDT Plus 2011;**4**:83-6. doi: 10.1093/ndtplus/sfq211. Epub 2011 January 27
15. Nyman HA, Dowling TC, Hudson JQ, Peter WL, Joy MS, Nolin TD. 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. doi: 10.1592/phco.31.11.1130.
16. Gouin-Thibault I, Pautas E, Mahé I et al. Is Modification of Diet in Renal Disease formula similar to Cockcroft-Gault formula to assess renal function in elderly

hospitalized patients treated with low-molecular-weight heparin? J Gerontol A Biol Sci Med Sci 2007;**62**:1300-5.

17. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group--a cautionary tale. Nephrol Dial Transplant 2007;**22**:2894-9. Epub 2007 Jun 16.
18. Helldén A, Bergman U, von Euler M, Hentschke M, Odar-Cederlöf I, Öhlén G. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. Drugs Aging 2009;**26**:595-606. doi: 10.2165/11315790-000000000-00000.
19. Frank M, Guarino-Gubler S, Burnier M, Maillard M, Keller F, Gabutti L. Estimation of glomerular filtration rate in hospitalised patients: are we overestimating renal function? Swiss Med Wkly 2012;**142**:0. doi: 10.4414/smw.2012.13708.
20. Helldén A, Odar-Cederlöf I, Diener P et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant 2003;**18**:1135-41.
21. Söderström A, Bergman U, Helldén A, Odar-Cederlöf I. Renal function and drug treatment in a home care center in Farsta (Abstract. In Swedish). Poster LÄ 2P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.
22. Johansson M, Bergman U, Helldén A, Mejyr S, Öhlén G. Adverse drug reaction-related admissions at the Karolinska University Hospital, Huddinge- a follow up with focus on generic drug treatment. (Abstract. In Swedish) Poster AM25P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.

23. Odar-Cederlöf I, Oskarsson P, Öhlén G et al. Adverse drug effect as cause of hospital admission. Common drugs are the major part according to the cross-sectional study (in Swedish). Läkartidningen 2008;**105**:890-3.

24. von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiol Drug Saf 2006;**15**:179-84.

25. Hedberg P, Lönnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. Eur Heart J 2001;**22**:676-83.

26. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010;**49**:259-68. doi: 10.2165/11318170-000000000-00000.

27. Levey AS, Coresh J, Greene T et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;**53**:766-72. Epub 2007 Mar 1.

28. Lamb EJ. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2005;**42**:160-1.

29. Dabigatran (Pradaxa): risk of bleeding relating to use. (www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm) (Accessed 2012-01-10).

30. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. Ann Pharmacother 2012;**46**:e10. doi: 10.1345/aph.1Q747. Epub 2012 Apr 10.

31. Denetclaw TH, Oshima N, Dowling TC. Dofetilide dose calculation errors in elderly associated with use of the modification of diet in renal disease equation. Ann Pharmacother 2011;**45**:e44 doi: 10.1345/aph.1Q159. Epub 2011 Jun 28.

32. Stevens L, Nolin T, Richardson M et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;**54**:33-42. 2009 Jul;54(1):33-42. doi: 10.1053/j.ajkd.2009.03.008. Epub 2009 May 17.

33. Wargo K, Eiland E3, Hamm W, English T, Phillippe H. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother 2006;**40**:1248-53. Epub 2006 Jul 11.

34. Spruill WJ, Wade WE, Cobb HH. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009;**86**:468-70. doi: 10.1038/clpt.2009.187.

35. Hermsen E, Maiefski M, Florescu M, Qiu F, Rupp M. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy 2009;**29**:649-55. doi: 10.1592/phco.29.6.649.

36. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134763.pdf (accessed 12-03-20).

37. Dabigatran SPC. http://www.medicines.org.uk/emc/medicine/20760/SPC/ (accessed 12-03-13).

38. Pradaxa EPAR- Product information. http://wwwemaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf (accessed 2012-03-13)

39. Eriksson BI, Dahl OE, Ahnfelt L et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. J Thromb Haemost 2004;**2**:1573-80.

40. Trocóniz I, Tillmann C, Liesenfeld K, Schäfer H, Stangier J. Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. J Clin Pharmacol 2007;**47**:371-82.

41. Lehr T, Haertter S, Liesenfeld KH et al. Dabigatran Etexilate in Atrial Fibrillation Patients with Severe Renal Impairment: Dose Identification Using Pharmacokinetic Modeling and Simulation. J Clin Pharmacol 2012;**52**:1373-8. doi: 10.1177/0091270011417716. Epub 2011 Sep 28.

42. Charhon N, Neely MN, Bourguignon L, Maire P, Jelliffe RW, Goutelle S. Comparison of Four Renal Function Estimation Equations for Pharmacokinetic Modeling of Gentamicin in Geriatric Patients Antimicrob Agents Chemother 2012;**56**:1862-9. doi: 10.1128/AAC.05634-11. Epub 2012 Jan 30.

43. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. N Engl J Med 2011;**365**:2039-40. doi: 10.1056/NEJMc1111095.

44. Tawadrous D, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis 2011;**58**:903-14. doi: 10.1053/j.ajkd.2011.07.022. Epub 2011 Sep 23.

45. Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf (Accessed 2013-01-31)

46. Chin PK, Vella-Brincat JW, Barclay ML, Begg EJ. Perspective on dabigatran etexilate dosing - why not follow standard pharmacological principles? Br J Clin Pharmacol 2012;74:734-40. doi: 10.1111/j.1365-2125.2012.04266.x.

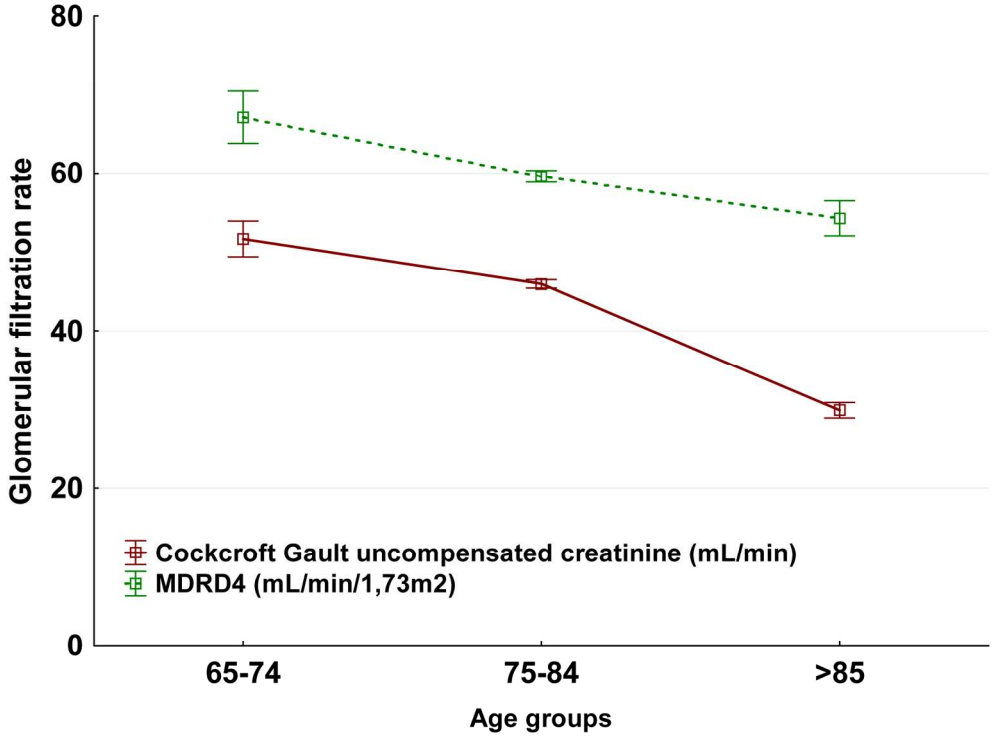

Figure 1. Renal function estimated in 790 individuals aged 65 and older by the Cockcroft & Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in mL/min) and MDRD4 calculated according to the equations in Table II. Estimated GFR (eGFR) is given as a relative value (mL/min/1.73m2). Mean ± SEM. Uncompensated creatinine denotes S/P-creatinine determined with the "old Jaffe" analysis.(13)

165x124mm (300 x 300 DPI)

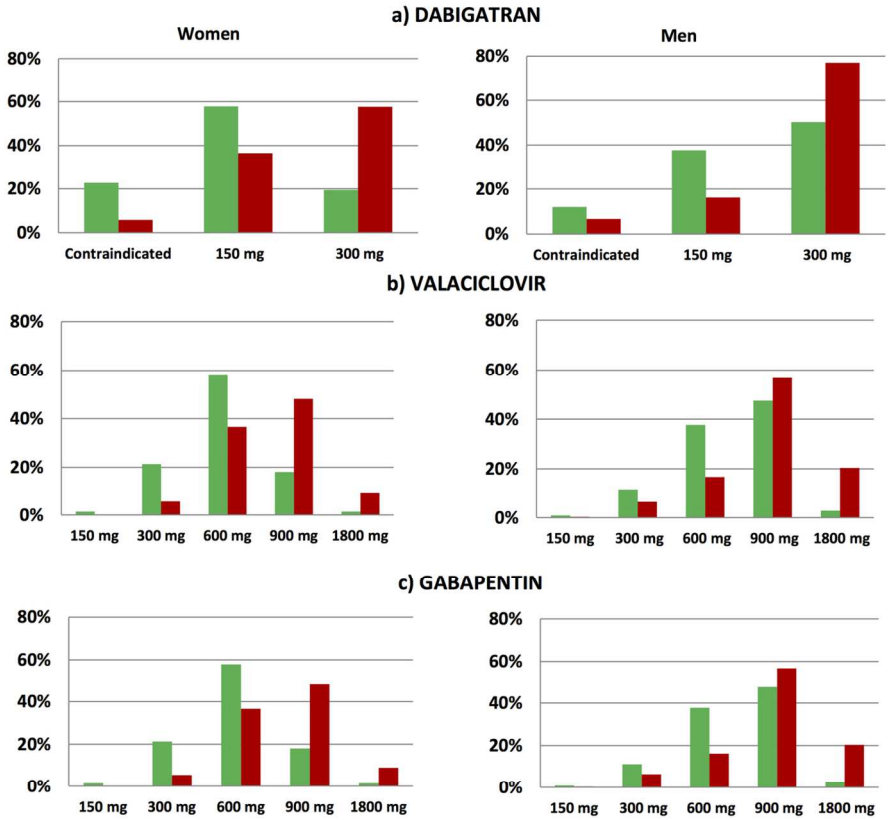

Figure 2 a-c. Data simulation of recommended daily doses for dabigatran (Figure 2 a), valaciclovir (Figure 2 b) and gabapentin (Figure 2 c) in relation to renal function by the Cockcroft-Gault formula (green staples) and the abbreviated Modification of Diet in Renal Disease (MDRD4) formula (red staples) in 790 subjects 65 years and older in Sweden. Dose recommendations by the MDRD4 formula will result in significantly higher doses, particularly in women. As an example, 19% (82) of the female subjects would receive an ordinary dose (300 mg) of dabigatran if the Cockcroft & Gault equation with uncompensated P-creatinine would be used when estimating renal function, compared to 59% (259) with the MDRD4 formula (Figure 2 a). Recommended daily dose for gabapentin is in general in a range from e.g. 900 - 3600 mg if creatinine clearance is higher than 80 mL/min. We have chosen to show half of the maximum recommended dose in each stratum.

128x117mm (300 x 300 DPI)

Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir. A data simulation study focusing on the elderly.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002686.R1
Article Type:	Research
Date Submitted by the Author:	20-Feb-2013
Complete List of Authors:	Helldén, Anders; Division of Clinical Pharmacology, Department of Laboratory Medicine Odar-Cederlöf, Ingegerd; Division of Clinical Pharmacology, Department of Laboratory Medicine Nilsson, Goran; Center for Clinical Research, Sjöviker, Susanne; Department of Drug Management and Informatics, Centre for Health Care Improvement, Stockholm County Council Söderström, Anders; Farsta home care center at the time of the study, von Euler, Mia; Division of Clinical Pharmacology, Department of Laboratory Medicine at the time of the study Öhlén, Gunnar; Quality and Patient Safety, Karolinska University Hospital Bergman, Ulf; Division of Clinical Pharmacology, of Laboratory Medicine
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Cardiovascular medicine, Neurology, Pharmacology and therapeutics, Renal medicine
Keywords:	Thromboembolism < CARDIOLOGY, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, Anticoagulation < HAEMATOLOGY, Adult nephrology < NEPHROLOGY, Stroke < NEUROLOGY

Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir. A data simulation study focusing on the elderly.

Anders Helldén *assistant consultant*[1], Ingegerd Odar-Cederlöf *associate professor*[1], Göran Nilsson *professor*[2], Susanne Sjöviker *research nurse*[3], Anders Söderström *general practitioner*[4], Mia von Euler *associate professor, senior medical officer*[5], Gunnar Öhlén *associate professor, chief medical officer*[6], Ulf Bergman *professor, senior medical officer*[1,7,8]

[1] At the Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, SE141 86 Stockholm, Sweden

[2]Centre of Clinical Research, Uppsala University, Centrallasarettet, 721 89 Västerås, Sweden;

[3]Department of Drug Management and Informatics, Centre for Health Care Improvement, Stockholm County Council, Stockholm, Sweden, at the time of the study;

[4]Farsta home care center at the time of the study, present at Vendelsö home care center, Stockholm, Sweden;

[5]Division of Clinical Pharmacology at the time of the study, present: Karolinska Institutet Stroke Research Network at Södersjukhuset, Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden;

[6]Department of Emergency Medicine, Karolinska University Hospital, Huddinge, at the time of the study, present Quality and Patient Safety, Karolinska University Hospital, Stockholm, Sweden;

[7]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden;

[8]Representative of the Division of Clinical Pharmacology, a partner in European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), coordinated by the European Medicines Agency (EMA)

Contact person: Anders Helldén, MD, PhD, Presently at the Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, 555 University Avenue, Toronto ON, M4P 0A2, Canada

Phone: +1-416-813-1500, extension 4414

Mobile: +1-647-838-5460

Mail: anders.hellden@ki.se

Number of words in abstract: 294

Number of words in manuscript: 2317

Number of figures: 2

Number of tables: 2

Key words: Cockcroft & Gault, ADR, bleeding, gabapentin, valaciclovir

ABSTRACT

Objectives: The thrombin inhibitor dabigatran is mainly excreted by the kidneys. We investigated whether the recommended method for estimation of renal function used in the clinical trials, the Cockcroft-Gault (CG_{old}) equation, and the (eGFR) MDRD4 equation, differ in elderly subjects, resulting in erroneously higher dose recommendations of dabigatran, which might explain the serious, even fatal, bleeding reported. The renally excreted drugs gabapentin and valaciclovir were also included for comparison.

Design: Retrospective data simulation study.

Participants: Subjects 65 years and older included in six different studies.

Main outcome measure: Estimated renal function by CG based on uncompensated ("old Jaffe") creatinine (CG_{old}) or by MDRD4 based on standardized compensated P-creatinine traceable to IDMS, and the resulting doses.

Results: 790 subjects (432 females), mean age (± SD) 77.6 ± 5.7 years. Mean estimated creatinine clearance (eCrCl) by the CG_{old} equation was 44.2 ± 14.8 mL/min, vs. estimated glomerular filtration rate (eGFR) 59.6 ± 20.7 mL/min/1.73 m^2 with MDRD4 ($P<0.001$), absolute median difference 13.5, 95% CI 12.9 to 14.2. MDRD4 gave a significantly higher mean dose (valaciclovir +21%, dabigatran +25%, and gabapentin +37%) of all drugs ($P<0.001$). With MDRD4 58% of the women would be recommended a full dose of dabigatran compared to 18% if CG_{old} is used.

Conclusion: MDRD4 would result in higher recommended doses of the three studied drugs to elderly subjects compared to CG, particularly in women, and thus increase the risk of dose and concentration-dependent adverse reactions. It is important to know which method of estimation of renal function the Summary of Products Characteristics was based on, and use only that one

when prescribing renally excreted drugs with narrow safety window, such as dabigatran. Doses based on recently developed methods for estimation of renal function may be associated with considerable risk of overtreatment in the elderly.

ARTICLE SUMMARY

Article focus

- The thrombin inhibitor dabigatran is eliminated by renal excretion. Severe bleeding, even fatal, was reported, mainly in elderly patients with impaired renal function.
- Dosing should be adjusted according to renal function, i.e. by the Cockcroft-Gault equation. However, in many countries the (eGFR) abbreviated Modification of Diet in Renal disease (MDRD4) equation is used in clinical practice for estimation of renal function.
- We studied whether use of MDRD4 would show different estimates and thus different recommended doses for dabigatran and for two other renally excreted drugs, gabapentin, and valaciclovir, in a group of elderly patients.

Key messages

- A significantly larger group of elderly subjects would receive a higher dose of the three drugs if MDRD4 was used for determination of dose. This may be one explanation of the cases of serious haemorrhage reported for dabigatran and CNS side effects for gabapentin and valaciclovir.
- A method to optimize ongoing therapy is to determine plasma concentrations of the drug – (TDM- Therapeutic Drug Monitoring).

Strengths and limitations of this study

- The main strength of this study is the number of elderly subjects and the different settings from where they were recruited, reflecting a mean of the older Swedish population.
- Limitations are that this is a data simulation study and no dabigatran, gabapentin, or valaciclovir dose has been given to the subjects.
- In addition, we have not performed any gold standard methods, such as iohexol clearance, to elucidate the true GFR in the studied subjects.

INTRODUCTION

The oral thrombin inhibitor dabigatran etexilate (Pradaxa®) is marketed as an alternative to warfarin for prevention of venous thromboembolism (VTE) in atrial fibrillation (AF). Dabigatran etexilate is a prodrug metabolized to the active species dabigatran, which is eliminated primarily by the kidneys. Renal function is therefore an important factor for its clearance rate.[1, 2]

Serious cases of hemorrhage, even fatal, have been reported with the drug,[3-5] mainly in elderly patients with severe renal impairment.[4, 6] Hemorrhage is a dose- and concentration-dependant adverse reaction, shown during the clinical trials with the drug, and the risk for hemorrhage increases in patients with low renal function.[7] To prevent this serious risk, renal function should be evaluated by estimation of creatinine clearance including age, sex, serum creatinine, and weight, based on the equation that was used during the clinical trials, presented as absolute values (mL/min) (Cockcroft-Gault- CG).[8] Later methods, such as the original Modification of Diet in Renal Disease (MDRD) equation, the abbreviated MDRD equation (MDRD4), and the Chronic Kidney Disease Epidemiology initiative (CKD-Epi) equation have been introduced providing estimates of glomerular filtration rate (eGFR) as a relative value of

mL/min/1.73m^2.[9-11] In many countries, MDRD4 is used in clinical practice. Recently, FDA draft guidance for industry suggested that both CG and MDRD can be used for pharmacokinetic studies in patients with impaired renal function.[1] The latter equation uses standardized serum creatinine concentrations traceable to Isotope-Dilution Mass Spectrometry (IDMS), resulting in a lower serum creatinine concentration (compensated) compared to the old Jaffe method (uncompensated).[12-15] The MDRD formula has shown to provide significantly higher eGFR values in the elderly, potentially increasing the risk for dabigatran-induced hemorrhages.[16-19] For the purpose of the present study we also studied two other drugs dependent on renal function; gabapentin, that is excreted unchanged by the kidneys, and valaciclovir, that forms a toxic metabolite in patients with renal impairment.[20]

SUBJECTS AND METHODS

Data from subjects 65 years and older were compiled from six different studies on renal function in the elderly. All subjects were Caucasians. One study was performed in a home care center (N=88)[21]: four studies were performed at an intermediary care unit of internal medicine within the emergency department (N=270),[18, 22-24] all in Stockholm; and finally one study of 75-year-old subjects was performed in the city of Västerås (N=432).[25] We simulated the doses of dabigatran that these subjects would be prescribed based on their renal function, i.e. 300 mg if creatinine clearance is higher than 50 mL/min; 220 mg if creatinine clearance is 30-50 mL/min and associated with high risk of bleeding; and finally contraindicated if creatinine clearance is less than 30 mL/min. The rationale behind our stratification is that exposure to dabigatran increases 3- and to 6-fold in patients with moderate and severe renal impairment.[26] Patient characteristics, such as weight, height, age, and sex were recorded. Complete data were retrieved for 790 subjects, 432 women and 358 men (Table I). Ethical approval was obtained for five studies; the sixth was a local quality assessment not

requiring ethical approval in Sweden. From the six studies, only laboratory and demographic data about the included subjects were received by the investigators and all other information was blinded.

Table 1. Demographic data (age, sex, weight, length, BSA= body surface area, BMI= body mass index) for 790 individuals aged 65 and older divided between men and women in Sweden from six different studies of the elderly. Renal function estimates with different methods: CG= Cockcroft & Gault. MDRD4= abbreviated Modification of Diet in Renal Disease equation. Divide by 88.4 to get creatinine concentration in mg/mL. Mean ± SD, P<0.05 is regarded as significant.

	All (N=790)	Female (N=432)	Male (N=358)	P-value
Age (years)	77.6 ± 5.7	78.0 ± 6.0	77.1 ± 5.2	0.022
Weight (kg)	70.2 ± 13.9	66.0 ± 14.0	75.2 ± 12.1	< 0.0001
Height (cm) (N=590)	167 ± 8.6	161.3 ± 5.5[a)]	174.0 ± 6.1[b)]	< 0.0001
BSA (m^2) (N=590)	1.8 ± 0.18	1.7 ± 0.17[a)]	1.9 ± 0.14[b)]	< 0.0001
BMI (N=590)	25.5 ± 4.2	25.7 ± 4.6[a)]	25.1 ± 3.5[b)]	0.073
Compensated P-creatinine (µmol/L)	102.2 ± 42.1	95.6 ± 35.0	110.1 ± 48.3	< 0.0001
Uncompensated P-creatinine (µmol/L)	120.2 ± 38.8	114.0 ± 32.2	127.3 ± 44.4	< 0.0001
CG uncompensated P-creatinine (mL/min)	44.2 ± 14.8	39.8 ± 13.2	49.5 ± 15.0	< 0.001
MDRD4 (mL/min/1.73m^2)	59.6 ± 20.7	55.3 ± 19.4	64.7 ± 21.0	< 0.001

[a)] N=322
[b)] N=268

Statistics

Statistical analysis was performed with Statistica (Statsoft, Tulsa). ANOVA was used to compare the difference in renal clearance in relation to age. Continuous variables are expressed as mean and standard deviation (SD).

Estimation of renal function and drug dosage

Plasma creatinine was analyzed at the laboratory of Clinical Chemistry at Karolinska University Hospital and at the laboratory of Chemistry at Västerås hospital with a modified Jaffe method, traceable to IDMS[27] and similar to an enzymatic method, i.e. "compensated" creatinine. These values have then been recalculated to "uncompensated" creatinine when used in the CG_{old} equation (uncompensated creatinine = compensated creatinine * 0.92+26) to resemble the CG results gained in the initial studies of dabigatran.[13, 28] In addition, we investigated if similar relation could be shown with two other older drugs with renal excretion; gabapentin and valaciclovir. Compensated creatinine has been incorporated in the MDRD4 equation (Table II). We then simulated the dabigatran, gabapentin and valaciclovir dose each subject would receive based on the resulting renal clearance. Estimated GFR (eGFR) is as usual given in relative value (mL/min/1.73m^2).

Table II. Estimations of renal function used in a cohort of elderly subjects by two different equations: The Cockcroft & Gault equation with uncompensated P-creatinine (CG_{old}) and the MDRD4 equation calculated with compensated creatinine traceable to IDMS. No correction factor for afro-Americans has been included as all subjects were Caucasians. P-creatinine concentration in µmol/L.

$$CG_{old} = \frac{1.23 \times (140 - age) \times weight}{(P - creatinine \times 0.92 + 26)} (\times 0.85\ female)\ \text{mL/min (absolute)}$$

$$MDRD4 = 175 \times \left(\frac{P - creatinine}{88.4}\right)^{-1.154} \times age^{-0.203} (\times 0.742\ female)\ \text{mL/min/1.73m}^2\ \text{(relative)}$$

RESULTS

Renal function decreased significantly ($p < 0.001$) in relation to increasing age for both estimations (Figure 1). CG_{old} produced the lowest estimated renal function, 44.2 ± 14.8

mL/min, and MDRD4 the highest, 59.6 ± 20.7 mL/min/1.73 m^2 (P<0.001), absolute mean difference 13.5, 95% CI 12.9 to 14.2 (Table I). A data simulation showed a significantly higher mean dose of dabigatran with MDRD than with CG_{old}: 260 ± 76 mg compared to 208 ± 103 mg (25% higher dose) (P<0.001). The difference was even more pronounced for women, 253 ± 73 mg for MDRD4 compared to 186 ± 105 mg for CG_{old} (+36%) and less for men, 267 ± 77 mg for MDRD4 compared to 234 ± 94 mg for CG_{old}, (+14%) but still highly significant (P<0.001). For women, the MDRD4 equation resulted in an increased dose compared to the CG_{old} in 221 subjects (51%), a lower dose in eight subjects (2%) and an unaltered dose in 203 subjects (47%). Dabigatran would be contraindicated (creatinine clearance less than 30 mL/min) in 18% of all subjects using CG_{old} and in 7% of those with the MDRD4 equation. Thirty-three per cent of all subjects would be recommended a full dose of dabigatran if CG_{old} is used, whereas the corresponding number for MDRD4 is 67% (Figure 2 a). The same pattern was shown for valaciclovir and gabapentin; mean valaciclovir dose calculated with CG_{old} was 2156 ± 699 mg compared to 2602 ± 603 mg with MDRD4 (21% higher dose) (P<0.001). Gabapentin mean dose was 663 ± 266 mg when calculated with CG_{old} compared to 910 ± 406 mg with the MDRD4 (+37%) (P<0.001) (Figure 2 b and 2 c).

DISCUSSION

Our study shows that the change from the CG equation with uncompensated P-creatinine by the Jaffe analysis method to the MDRD4 equation with a compensated creatinine traceable to IDMS, results in significantly higher renal function value in the elderly. Consequently the dose recommendation based on MDRD4 results in higher doses of dabigatran, particularly in elderly female subjects. This may have contributed to the serious and sometimes fatal adverse drug reactions (ADRs) reported around the world.[4, 6, 29, 30] We found similar results for two

older renally excreted drugs (also developed during a period when uncompensated creatinine by the Jaffe creatinine method was used), valaciclovir and gabapentin for comparison.

The problem is similar to that which would be faced when treating patients with other renally excreted drugs (including metabolites) e.g. antibiotics, pregabalin, metformin, and morphine. Other researchers have found similar results.[15-17, 31] There are reports suggesting that MDRD can be used for drug dosing,[32] whereas others have questioned it.[33-35]

In Europe, a "Dear Healthcare Professional Letter" was circulated in October 2011 to point out that renal function should be estimated in all patients before treatment with dabigatran. This recommendation was released in order to exclude those patients with creatinine clearance less than 30 ml/min, where dabigatran is contraindicated due to increased risk of bleeding.[36] Renal function should be re-estimated in clinical situations where renal function may decline and at least annually in patients older than 75 years (corresponding to 29% of all dabigatran users in Sweden). The current European dabigatran Summary of Products Characteristics (SPC) points out that in patients with advanced age and moderately impaired renal function (creatinine clearance 30 – 50 ml/min) dose reduction should be considered and the patients should be closely observed regarding bleeding or anemia.[37]

Dose recommendations in relation to renal function given in the SPCs are in general based on endogenous creatinine clearance or estimated creatinine clearance according to the CG equation (including P-creatinine, age, sex, and weight) in mL/min, an absolute value of clearance.[1] This is also the case for dabigatran.[38] Different equations have been used in the trials such as the CG equation,[39-41] the original MDRD equation,[7, 9] measured creatinine clearance, and sinistrin clearance.[26] In one study only creatinine clearance is mentioned, without stating the clearance estimation method.[41] Since then, worldwide standardisation of the creatinine method has resulted in a lower reference range for creatinine and thus higher

clearance values in patients with low P-creatinine, e.g. elderly patients. Other researchers have also pointed out the differences among results from the various methods to estimate renal function and the consequential differences in doses.[15, 17, 31, 42]

The "Dear Healthcare Professional Letter" states that dose recommendations should be based on equations based on sex, age, and weight.[36] This statement excludes the MDRD4 equation and the CKD-Epi equation as they do not include weight in the calculation. With MDRD4 (we found similar results with the CKD-Epi formula- data not shown) more patients will be recommended higher doses of dabigatran than with CG and will be exposed to greater risk of dose-concentration dependent adverse drug reactions, e.g. hemorrhage. There is no antidote to give if the dose is too high, nor in trauma or acute operations. The only treatment available presently is symptomatic or possibly dialysis.[43]

Another important factor is to use the patient's absolute renal function and not the relative clearance the patient or subject would have had if his/her body surface area would have been 1.73 m^2 since most dose recommendations based on dose-effect studies use the absolute clearance.[34] "Absolute"= without correction for body surface area (mL/min) and "relative"= with correction for body surface area (mL/min/1.73m^2). In most patients, the difference between the two may be small but in certain patients, e.g. elderly women, in particular those with a body surface area (BSA) smaller than (the standard) 1.73 m^2, the difference may be considerable. A case report from France describes two elderly dabigatran-treated women 84 and 89 years old, respectively, one with a fatal and one with a serious hemorrhage. Plasma concentrations of dabigatran were reported to be high. Both patients had low weight, low relative creatinine clearance of 29 and 32 mL/min/1.73 m^2, respectively, and probably an absolute creatinine clearance below 30 ml/min, which is a contraindication for dabigatran treatment.[4]

For older remedies to prevent dangerously high doses in the elderly a comparison factor between older and newer methods to determine P-creatinine may be needed, however impractical. We found that the method used to estimate renal function has impact on recommended dabigatran doses in the elderly. Subsequently, one question remains to be answered; Can we rely on the measurements of renal function made in the initial dabigatran pharmacokinetic studies? This needs urgently to be elucidated for the elderly.

Elderly patients with decreased renal function are at particular risk for dose- and concentration-dependent ADRs. Their reduced renal function is not always noticed.[18] There is a great need of evidence-based support when prescribing drugs for elderly patients.[44] Before new methods to estimate renal function, e.g. MDRD4 and CKD-EPI, all being surrogate markers for renal function, are used for drug dosing in the elderly, the consequences must be well documented, including pharmacokinetic modeling and TDM (Therapeutic Drug Monitoring). In the most recent draft guideline from the US-FDA, both CG and MDRD4 may be used.[1] The current "Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function" from EMEA 2004 states that measuring GFR should be based on accurate well established methods (such as iohexol clearance).[45] In contrast to the US-FDA, there is no practical recommendation from EMA.

We support that recommended dabigatran dose-rate should be adjusted linearly for decreases in creatinine clearance and standard pharmacological principles.[46] We also suggest that the therapy in the elderly is more frequently guided by TDM, if available.

CONCLUSION

This data simulation study shows that the MDRD4 equation would result in higher doses of dabigatran, gabapentin, and valaciclovir to elderly subjects, particularly in women, compared to

the CG equation that was used during the clinical trials, and thus increase the risk of dose and concentration-dependent ADRs. Although dose recommendations for dabigatran in the SPC refer to both renal function and age, creatinine clearance according to CG is the basis for calculating recommended doses for dabigatran as for many other drugs with renal elimination. Doses based on other methods may be associated with considerable risk.

ACKNOWLEDGEMENTS

We are grateful to Maria Hentschke, RN, for her skilful contribution with the collection of patient data, and to Professor Gideon Koren, who provided valuable comments to the final manuscript.

Contributions: AH, I O-C and UB initiated, designed and analysed the data and wrote the article.

GN, SS, AS, MvE, GÖ contributed with the collection and evaluation of patient data. All authors interpreted the data, critically revised the manuscript, and gave final approval of the version to be published. AH is the guarantor.

Funding: This study was supported by the Stockholm County Council (ALF 20060747, FOU project no. 560747) and by grants from the Karolinska Institutet.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Data Sharing: There are no additional unpublished data from the study.

REFERENCES:

1. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. DRAFT GUIDANCE http://wwwfdagov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf 2010 (accessed 2012-02-03).
2. PRADAXA, EPAR. Summary for the public. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/medicines/human/medicines/000829/human_med_000981jsp&murl=menus/medicines/medicinesjsp&jsenabled=true (accessed 2012-10-28).
3. Casado Naranjo I, Portilla-Cuenca J, Jiménez Caballero P, et al. Fatal intracerebral hemorrhage associated with administration of recombinant tissue plasminogen activator in a stroke patient on treatment with dabigatran. Cerebrovasc Dis 2011;**32**:616-9. doi: 10.1159/000334578. Epub 2011 Dec 1.
4. Legrand M, Mateo J, Aribaud A et al. The use of dabigatran in elderly patients. Arch Intern Med 2011;**171**:1285-6. doi: 10.1001/archinternmed.2011.314.
5. Chen B, Viny A, Garlich F et al. Hemorrhagic complications associated with dabigatran use. Clin Toxicol 2012;**50**:854-7. doi: 10.3109/15563650.2012.721888. Epub 2012 Sep 12.
6. Food and Drug Administration. www.fda.gov/Drugs/DrugSafety/ucm282724.htm (accessed 12-02-03).
7. Ezekowitz MD, Reilly PA, Nehmiz G et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;**100**:1419-26. Epub 2007 Aug 17.

8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;**16**:31-41.
9. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;**130**:461-70.
10. Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;**145**:247-54.
11. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;**150**:604-12.
12. Wuyts B, Bernard D, Van den Noortgate N et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. Clin Chem 2003;**49**:1011-4.
13. Chan MH, Ng KF, Szeto CC et al. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2004;**41**:482-4.
14. Delanghe J, Speeckaert M. Creatinine determination according to Jaffe- what does it stand for? NDT Plus 2011;**4**:83-6. doi: 10.1093/ndtplus/sfq211. Epub 2011 January 27
15. 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. doi: 10.1592/phco.31.11.1130.
16. Gouin-Thibault I, Pautas E, Mahé I et al. Is Modification of Diet in Renal Disease formula similar to Cockcroft-Gault formula to assess renal function in elderly

hospitalized patients treated with low-molecular-weight heparin? J Gerontol A Biol Sci Med Sci 2007;**62**:1300-5.

17. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group--a cautionary tale. Nephrol Dial Transplant 2007;**22**:2894-9. Epub 2007 Jun 16.
18. Helldén A, Bergman U, von Euler M, et al. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. Drugs Aging 2009;**26**:595-606. doi: 10.2165/11315790-000000000-00000.
19. Frank M, Guarino-Gubler S, Burnier M, et al. Estimation of glomerular filtration rate in hospitalised patients: are we overestimating renal function? Swiss Med Wkly 2012;**142**:0. doi: 10.4414/smw.2012.13708.
20. Helldén A, Odar-Cederlöf I, Diener P et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant 2003;**18**:1135-41.
21. Söderström A, Bergman U, Helldén A, et al. Renal function and drug treatment in a home care center in Farsta (Abstract. In Swedish). Poster LÄ 2P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.
22. Johansson M, Bergman U, Helldén A, et al. Adverse drug reaction-related admissions at the Karolinska University Hospital, Huddinge- a follow up with focus on generic drug treatment. (Abstract. In Swedish) Poster AM25P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.
23. Odar-Cederlöf I, Oskarsson P, Öhlén G et al. Adverse drug effect as cause of hospital admission. Common drugs are the major part according to the cross-sectional study (in Swedish). Läkartidningen 2008;**105**:890-3.

24. von Euler M, Eliasson E, Öhlén G, et al. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiol Drug Saf 2006;**15**:179-84.

25. Hedberg P, Lönnberg I, Jonason T, et al. Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. Eur Heart J 2001;**22**:676-83.

26. Stangier J, Rathgen K, Stähle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010;**49**:259-68. doi: 10.2165/11318170-000000000-00000.

27. Levey AS, Coresh J, Greene T et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;**53**:766-72. Epub 2007 Mar 1.

28. Lamb EJ. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2005;**42**:160-1.

29. Dabigatran (Pradaxa): risk of bleeding relating to use. (www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm) (Accessed 2012-01-10).

30. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. Ann Pharmacother 2012;**46**:e10. doi: 10.1345/aph.1Q747. Epub 2012 Apr 10.

31. Denetclaw TH, Oshima N, Dowling TC. Dofetilide dose calculation errors in elderly associated with use of the modification of diet in renal disease equation. Ann Pharmacother 2011;**45**:e44 doi: 10.1345/aph.1Q159. Epub 2011 Jun 28.

32. Stevens L, Nolin T, Richardson M et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis

2009;**54**:33-42. 2009 Jul;54(1):33-42. doi: 10.1053/j.ajkd.2009.03.008. Epub 2009 May 17.

33. Wargo K, Eiland E3, Hamm W, et al. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother 2006;**40**:1248-53. Epub 2006 Jul 11.
34. Spruill WJ, Wade WE, Cobb HH. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009;**86**:468-70. doi: 10.1038/clpt.2009.187.
35. Hermsen E, Maiefski M, Florescu M, et al. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy 2009;**29**:649-55. doi: 10.1592/phco.29.6.649.
36. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134763.pdf (accessed 12-03-20).
37. Dabigatran S. http://www.medicines.org.uk/emc/medicine/20760/SPC/ (accessed 12-03-13).
38. Pradaxa EPAR- Product information. http://wwwemaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf (accessed 2012-03-13)
39. Eriksson BI, Dahl OE, Ahnfelt L et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. J Thromb Haemost 2004;**2**:1573-80.
40. Trocóniz I, Tillmann C, Liesenfeld K, et al. Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. J Clin Pharmacol 2007;**47**:371-82.

41. Lehr T, Haertter S, Liesenfeld KH et al. Dabigatran Etexilate in Atrial Fibrillation Patients with Severe Renal Impairment: Dose Identification Using Pharmacokinetic Modeling and Simulation. J Clin Pharmacol 2012;**52**:1373-8. doi: 10.1177/0091270011417716. Epub 2011 Sep 28.

42. Charhon N, Neely MN, Bourguignon L, et al. Comparison of Four Renal Function Estimation Equations for Pharmacokinetic Modeling of Gentamicin in Geriatric Patients Antimicrob Agents Chemother 2012;**56**:1862-9. doi: 10.1128/AAC.05634-11. Epub 2012 Jan 30.

43. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. N Engl J Med 2011;**365**:2039-40. doi: 10.1056/NEJMc1111095.

44. Tawadrous D, Shariff SZ, Haynes RB, et al. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis 2011;**58**:903-14. doi: 10.1053/j.ajkd.2011.07.022. Epub 2011 Sep 23.

45. Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf (Accessed 2013-01-31)

46. Chin PK, Vella-Brincat JW, Barclay ML, et al. Perspective on dabigatran etexilate dosing - why not follow standard pharmacological principles? Br J Clin Pharmacol 2012;74:734-40. doi: 10.1111/j.1365-2125.2012.04266.x.

LEGENDS .

Figure 1. Renal function estimated in 790 individuals aged 65 and older by the Cockcroft & Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in mL/min) and MDRD4 calculated according to the equations in Table II. Estimated GFR (eGFR) is given as a relative value (mL/min/1.73m^2). Mean ± SEM. Uncompensated creatinine denotes S/P-creatinine determined with the "old Jaffe" analysis.(13)

Figure 2 a-c. Data simulation of recommended daily doses for dabigatran (Figure 2 a), valaciclovir (Figure 2 b) and gabapentin (Figure 2 c) in relation to renal function by the Cockcroft-Gault formula (green staples) and the abbreviated Modification of Diet in Renal Disease (MDRD4) formula (red staples) in 790 subjects 65 years and older in Sweden. Dose recommendations by the MDRD4 formula will result in significantly higher doses, particularly in women. As an example, 19% (82) of the female subjects would receive an ordinary dose (300 mg) of dabigatran if the Cockcroft & Gault equation with uncompensated P-creatinine would be used when estimating renal function, compared to 59% (259) with the MDRD4 formula (Figure 2 a). Recommended daily dose for gabapentin is in general in a range from e.g. 900 - 3600 mg if creatinine clearance is higher than 80 mL/min. We have chosen to show half of the maximum recommended dose in each *stratum*.

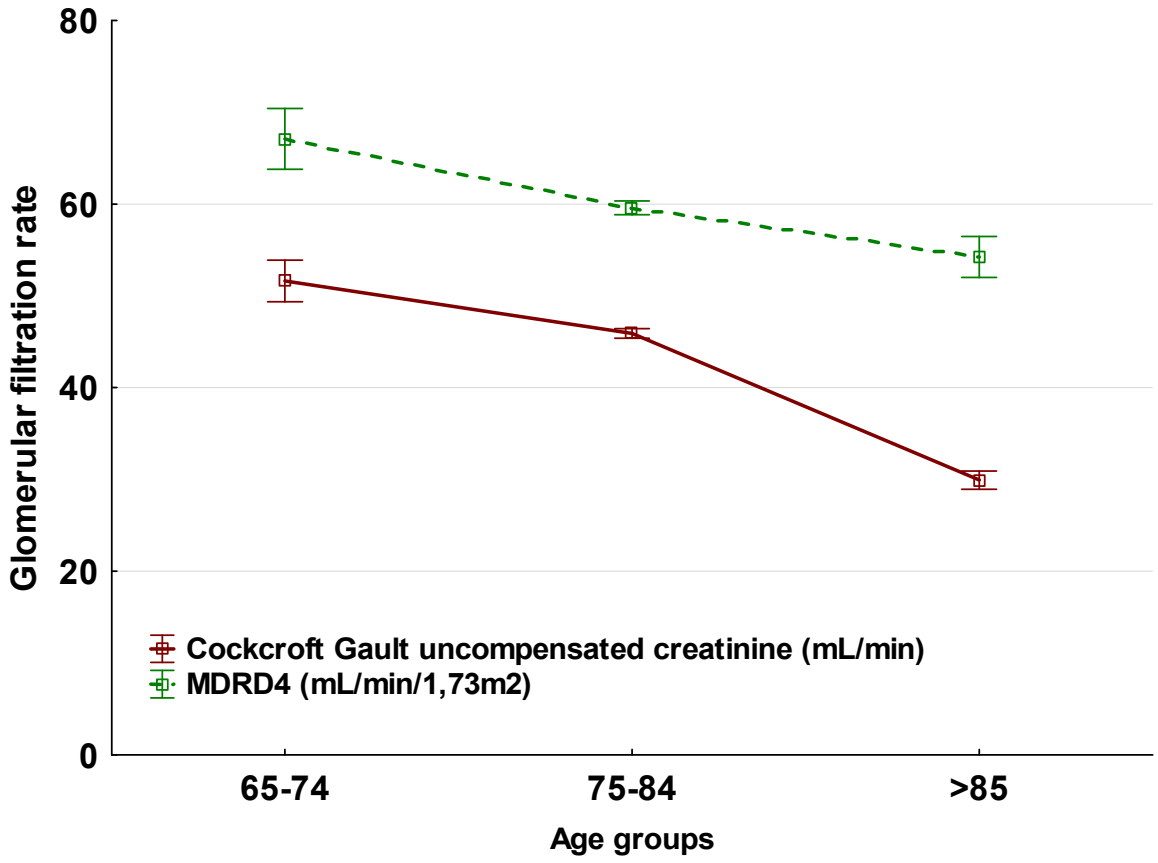

Figure 1.

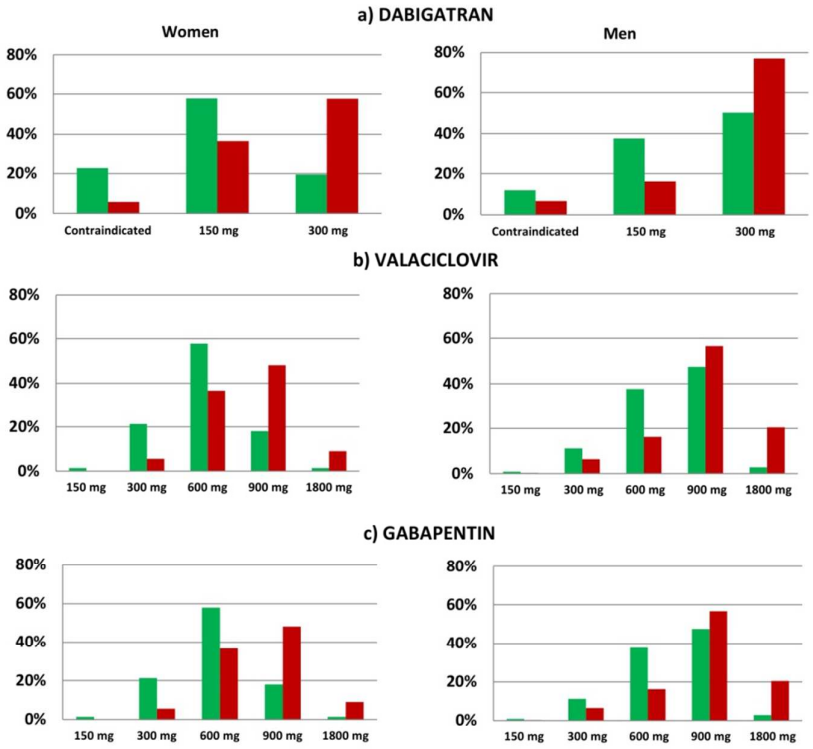

Figure 2 a-c)

~~Dangerously~~ Potentially dangerous higher recommended doses of dabigatran in the elderly, particularly in women, with the use of the MDRD4 formula to estimate glomerular filtration rate: A data simulation study.

Anders Helldén *assistant consultant*[1], Ingegerd Odar-Cederlöf *associate professor*[1], Göran Nilsson *professor*[2], Susanne Sjöviker *research nurse*[3], Anders Söderström *general practitioner*[4], Mia von Euler *associate professor, senior medical officer*[5], Gunnar Öhlén *associate professor, chief medical officer*[6], Ulf Bergman *professor, senior medical officer*[1,7,8]

[1] At the Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, SE141 86 Stockholm, Sweden

[2]Centre of Clinical Research, Uppsala University, Centrallasarettet, 721 89 Västerås, Sweden;

[3]Department of Drug Management and Informatics, Centre for Health Care Improvement, Stockholm County Council, Stockholm, Sweden, at the time of the study;

[4]Farsta home care center at the time of the study, present at Vendelsö home care center, Stockholm, Sweden;

[5]Division of Clinical Pharmacology at the time of the study, present: Karolinska Institutet Stroke Research Network at Södersjukhuset, Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden;

[6]Department of Emergency Medicine, Karolinska University Hospital, Huddinge, at the time of the study, present Quality and Patient Safety, Karolinska University Hospital, Stockholm, Sweden;

[7]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden;

[8]Representative of the Division of Clinical Pharmacology, a partner in European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), coordinated by the European Medicines Agency (EMA)

Contact person: Anders Helldén, MD, PhD, Presently at the Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, 555 University Avenue, Toronto ON, M4P 0A2, Canada

Phone: +1-416-813-1500, extension 4414

Mobile: +1-647-838-5460

Mail: anders.hellden@ki.se

Number of words in abstract: 294

Number of words in manuscript: 2317

Number of figures: 2

Number of tables: 2

Key words: Cockcroft & Gault, ADR, bleeding, gabapentin, valaciclovir

ABSTRACT

Objectives: The thrombin inhibitor dabigatran is mainly excreted by the kidneys. We investigated whether the recommended method for estimation of renal function used in the clinical trials, the Cockcroft-Gault (CG_{old}) equation, and the (eGFR) MDRD4 equation, differ in elderly subjects, resulting in erroneously higher dose recommendations of dabigatran, which might explain the serious, even fatal, bleeding reported. The renally excreted drugs gabapentin and valaciclovir were also included for comparison.

Design: Retrospective data simulation study.

Participants: Subjects 65 years and older included in six different studies.

Main outcome measure: Estimated renal function by CG based on uncompensated ("old Jaffe") creatinine (CG_{old}) or by MDRD4 based on standardized compensated P-creatinine traceable to IDMS, and the resulting doses.

Results: 790 subjects (432 females), mean age (± SD) 77.6 ± 5.7 years. Mean estimated creatinine clearance (eCrCl) by the CG_{old} equation was 44.2 ± 14.8 mL/min, vs. estimated glomerular filtration rate (eGFR) 59.6 ± 20.7 mL/min/1.73 m^2 with MDRD4 ($P<0.001$), absolute median difference 13.5, 95% CI 12.9 to 14.2. MDRD4 gave a significantly higher mean dose (valaciclovir +21%, dabigatran +25%, and gabapentin +37%) of all drugs ($P<0.001$). With MDRD4 58% of the women would be recommended a full dose of dabigatran compared to 18% if CG_{old} is used.

Conclusion: MDRD4 would result in higher recommended doses of the three studied drugs to elderly subjects compared to CG, particularly in women, and thus increase the risk of dose and concentration-dependent adverse reactions. It is important to know which method of estimation of renal function the Summary of Products Characteristics was based on, and use only that one

when prescribing renally excreted drugs with narrow safety window, such as dabigatran. Doses based on recently developed methods for estimation of renal function may be associated with considerable risk of overtreatment in the elderly.

ARTICLE SUMMARY

Article focus

- The thrombin inhibitor dabigatran is eliminated by renal excretion. Severe bleeding, even fatal, was reported, mainly in elderly patients with impaired renal function.
- Dosing should be adjusted according to renal function, i.e. by the Cockcroft-Gault equation. However, in many countries the (eGFR) abbreviated Modification of Diet in Renal disease (MDRD4) equation is used in clinical practice for estimation of renal function.
- We studied whether use of MDRD4 would show different estimates and thus different recommended doses for dabigatran and for two other renally excreted drugs, gabapentin, and valaciclovir, in a group of elderly patients.

Key messages

- A significantly larger group of elderly subjects would receive a higher dose of the three drugs if MDRD4 was used for determination of dose. This may be one explanation of the cases of serious haemorrhage reported for dabigatran and CNS side effects for gabapentin and valaciclovir.
- A method to optimize ongoing therapy is to determine plasma concentrations of the drug – (TDM- Therapeutic Drug Monitoring).

Strengths and limitations of this study

- The main strength of this study is the number of elderly subjects and the different settings from where they were recruited, reflecting a mean of the older Swedish population.
- Limitations are that this is a data simulation study and no dabigatran, gabapentin, or valaciclovir dose has been given to the subjects.
- In addition, we have not performed any gold standard methods, such as iohexol clearance, to elucidate the true GFR in the studied subjects.

INTRODUCTION

The oral thrombin inhibitor dabigatran etexilate (Pradaxa®) is marketed as an alternative to warfarin for prevention of venous thromboembolism (VTE) in atrial fibrillation (AF). Dabigatran etexilate is a prodrug metabolized to the active species dabigatran, which is eliminated primarily by the kidneys. Renal function is therefore an important factor for its clearance rate.[1, 2]

Serious cases of hemorrhage, even fatal, have been reported with the drug,[3-5] mainly in elderly patients with severe renal impairment.[4, 6] Hemorrhage is a dose- and concentration-dependant adverse reaction, shown during the clinical trials with the drug, and the risk for hemorrhage increases in patients with low renal function.[7] To prevent this serious risk, renal function should be evaluated by estimation of creatinine clearance including age, sex, serum creatinine, and weight, based on the equation that was used during the clinical trials, presented as absolute values (mL/min) (Cockcroft-Gault- CG).[8] Later methods, such as the original Modification of Diet in Renal Disease (MDRD) equation, the abbreviated MDRD equation (MDRD4), and the Chronic Kidney Disease Epidemiology initiative (CKD-Epi) equation have been introduced providing estimates of glomerular filtration rate (eGFR) as a relative value of

mL/min/1.73m^2.[9-11] In many countries, MDRD4 is used in clinical practice. Recently, FDA draft guidance for industry suggested that both CG and MDRD can be used for pharmacokinetic studies in patients with impaired renal function.[1] The latter equation uses standardized serum creatinine concentrations traceable to Isotope-Dilution Mass Spectrometry (IDMS), resulting in a lower serum creatinine concentration (compensated) compared to the old Jaffe method (uncompensated).[12-15] The MDRD formula has shown to provide significantly higher eGFR values in the elderly, potentially increasing the risk for dabigatran-induced hemorrhages.[16-19] For the purpose of the present study we also studied two other drugs dependent on renal function; gabapentin, that is excreted unchanged by the kidneys, and valaciclovir, that forms a toxic metabolite in patients with renal impairment.[20]

SUBJECTS AND METHODS

Data from subjects 65 years and older were compiled from six different studies on renal function in the elderly. All subjects were Caucasians. One study was performed in a home care center (N=88)[21]: four studies were performed at an intermediary care unit of internal medicine within the emergency department (N=270),[18, 22-24] all in Stockholm; and finally one study of 75-year-old subjects was performed in the city of Västerås (N=432).[25] We simulated the doses of dabigatran that these subjects would be prescribed based on their renal function, i.e. 300 mg if creatinine clearance is higher than 50 mL/min; 220 mg if creatinine clearance is 30-50 mL/min and associated with high risk of bleeding; and finally contraindicated if creatinine clearance is less than 30 mL/min. The rationale behind our stratification is that exposure to dabigatran increases 3- and to 6-fold in patients with moderate and severe renal impairment.[26] Patient characteristics, such as weight, height, age, and sex were recorded. Complete data were retrieved for 790 subjects, 432 women and 358 men (Table I). Ethical approval was obtained for five studies; the sixth was a local quality assessment not

requiring ethical approval in Sweden. From the six studies, only laboratory and demographic data about the included subjects were received by the investigators and all other information was blinded.

Table 1. Demographic data (age, sex, weight, length, BSA= body surface area, BMI= body mass index) for 790 individuals aged 65 and older divided between men and women in Sweden from six different studies of the elderly. Renal function estimates with different methods: CG= Cockcroft & Gault. MDRD4= abbreviated Modification of Diet in Renal Disease equation. Divide by 88.4 to get creatinine concentration in mg/mL. Mean ± SD, P<0.05 is regarded as significant.

	All (N=790)	Female (N=432)	Male (N=358)	P-value
Age (years)	77.6 ± 5.7	78.0 ± 6.0	77.1 ± 5.2	0.022
Weight (kg)	70.2 ± 13.9	66.0 ± 14.0	75.2 ± 12.1	< 0.0001
Height (cm) (N=590)	167 ± 8.6	161.3 ± 5.5[a)]	174.0 ± 6.1[b)]	< 0.0001
BSA (m^2) (N=590)	1.8 ± 0.18	1.7 ± 0.17[a)]	1.9 ± 0.14[b)]	< 0.0001
BMI (N=590)	25.5 ± 4.2	25.7 ± 4.6[a)]	25.1 ± 3.5[b)]	0.073
Compensated P-creatinine (µmol/L)	102.2 ± 42.1	95.6 ± 35.0	110.1 ± 48.3	< 0.0001
Uncompensated P-creatinine (µmol/L)	120.2 ± 38.8	114.0 ± 32.2	127.3 ± 44.4	< 0.0001
CG uncompensated P-creatinine (mL/min)	44.2 ± 14.8	39.8 ± 13.2	49.5 ± 15.0	< 0.001
MDRD4 (mL/min/1.73m^2)	59.6 ± 20.7	55.3 ± 19.4	64.7 ± 21.0	< 0.001

[a)] N=322
[b)] N=268

Statistics

Statistical analysis was performed with Statistica (Statsoft, Tulsa). ANOVA was used to compare the difference in renal clearance in relation to age. Continuous variables are expressed as mean and standard deviation (SD).

Estimation of renal function and drug dosage

Plasma creatinine was analyzed at the laboratory of Clinical Chemistry at Karolinska University Hospital and at the laboratory of Chemistry at Västerås hospital with a modified Jaffe method, traceable to IDMS[27] and similar to an enzymatic method, i.e. "compensated" creatinine. These values have then been recalculated to "uncompensated" creatinine when used in the CG_{old} equation (uncompensated creatinine = compensated creatinine * 0.92+26) to resemble the CG results gained in the initial studies of dabigatran.[13, 28] In addition, we investigated if similar relation could be shown with two other older drugs with renal excretion; gabapentin and valaciclovir. Compensated creatinine has been incorporated in the MDRD4 equation (Table II). We then simulated the dabigatran, gabapentin and valaciclovir dose each subject would receive based on the resulting renal clearance. Estimated GFR (eGFR) is as usual given in relative value (mL/min/1.73m^2).

Table II. Estimations of renal function used in a cohort of elderly subjects by two different equations: The Cockcroft & Gault equation with uncompensated P-creatinine (CG_{old}) and the MDRD4 equation calculated with compensated creatinine traceable to IDMS. No correction factor for afro-Americans has been included as all subjects were Caucasians. P-creatinine concentration in µmol/L.

$$CG_{old} = \frac{1.23 \times (140 - age) \times weight}{(P - creatinine \times 0.92 + 26)} (\times 0.85\ female)\ \text{mL/min (absolute)}$$

$$MDRD4 = 175 \times \left(\frac{P - creatinine}{88.4}\right)^{-1.154} \times age^{-0.203} (\times 0.742\ female)\ \text{mL/min/1.73m}^2\ \text{(relative)}$$

RESULTS

Renal function decreased significantly ($p < 0.001$) in relation to increasing age for both estimations (Figure 1). CG_{old} produced the lowest estimated renal function, 44.2 ± 14.8

mL/min, and MDRD4 the highest, 59.6 ± 20.7 mL/min/1.73 m^2 (P<0.001), absolute mean difference 13.5, 95% CI 12.9 to 14.2 (Table I). A data simulation showed a significantly higher mean dose of dabigatran with MDRD than with CG_{old}: 260 ± 76 mg compared to 208 ± 103 mg (25% higher dose) (P<0.001). The difference was even more pronounced for women, 253 ± 73 mg for MDRD4 compared to 186 ± 105 mg for CG_{old} (+36%) and less for men, 267 ± 77 mg for MDRD4 compared to 234 ± 94 mg for CG_{old}, (+14%) but still highly significant (P<0.001). For women, the MDRD4 equation resulted in an increased dose compared to the CG_{old} in 221 subjects (51%), a lower dose in eight subjects (2%) and an unaltered dose in 203 subjects (47%). Dabigatran would be contraindicated (creatinine clearance less than 30 mL/min) in 18% of all subjects using CG_{old} and in 7% of those with the MDRD4 equation. Thirty-three per cent of all subjects would be recommended a full dose of dabigatran if CG_{old} is used, whereas the corresponding number for MDRD4 is 67% (Figure 2 a). The same pattern was shown for valaciclovir and gabapentin; mean valaciclovir dose calculated with CG_{old} was 2156 ± 699 mg compared to 2602 ± 603 mg with MDRD4 (21% higher dose) (P<0.001). Gabapentin mean dose was 663 ± 266 mg when calculated with CG_{old} compared to 910 ± 406 mg with the MDRD4 (+37%) (P<0.001) (Figure 2 b and 2 c).

DISCUSSION

Our study shows that the change from the CG equation with uncompensated P-creatinine by the Jaffe analysis method to the MDRD4 equation with a compensated creatinine traceable to IDMS, results in significantly higher renal function value in the elderly. Consequently the dose recommendation based on MDRD4 results in higher doses of dabigatran, particularly in elderly female subjects. This may have contributed to the serious and sometimes fatal adverse drug reactions (ADRs) reported around the world.[4, 6, 29, 30] We found similar results for two

older renally excreted drugs (also developed during a period when uncompensated creatinine by the Jaffe creatinine method was used), valaciclovir and gabapentin for comparison.

The problem is similar to that which would be faced when treating patients with other renally excreted drugs (including metabolites) e.g. antibiotics, pregabalin, metformin, and morphine. Other researchers have found similar results.[15-17, 31] There are reports suggesting that MDRD can be used for drug dosing,[32] whereas others have questioned it.[33-35]

In Europe, a "Dear Healthcare Professional Letter" was circulated in October 2011 to point out that renal function should be estimated in all patients before treatment with dabigatran. This recommendation was released in order to exclude those patients with creatinine clearance less than 30 ml/min, where dabigatran is contraindicated due to increased risk of bleeding.[36] Renal function should be re-estimated in clinical situations where renal function may decline and at least annually in patients older than 75 years (corresponding to 29% of all dabigatran users in Sweden). The current European dabigatran Summary of Products Characteristics (SPC) points out that in patients with advanced age and moderately impaired renal function (creatinine clearance 30 – 50 ml/min) dose reduction should be considered and the patients should be closely observed regarding bleeding or anemia.[37]

Dose recommendations in relation to renal function given in the SPCs are in general based on endogenous creatinine clearance or estimated creatinine clearance according to the CG equation (including P-creatinine, age, sex, and weight) in mL/min, an absolute value of clearance.[1] This is also the case for dabigatran.[38] Different equations have been used in the trials such as the CG equation,[39-41] the original MDRD equation,[7, 9] measured creatinine clearance, and sinistrin clearance.[26] In one study only creatinine clearance is mentioned, without stating the clearance estimation method.[41] Since then, worldwide standardisation of the creatinine method has resulted in a lower reference range for creatinine and thus higher

clearance values in patients with low P-creatinine, e.g. elderly patients. Other researchers have also pointed out the differences among results from the various methods to estimate renal function and the consequential differences in doses.[15, 17, 31, 42]

The "Dear Healthcare Professional Letter" states that dose recommendations should be based on equations based on sex, age, and weight.[36] This statement excludes the MDRD4 equation and the CKD-Epi equation as they do not include weight in the calculation. With MDRD4 (we found similar results with the CKD-Epi formula- data not shown) more patients will be recommended higher doses of dabigatran than with CG and will be exposed to greater risk of dose-concentration dependent adverse drug reactions, e.g. hemorrhage. There is no antidote to give if the dose is too high, nor in trauma or acute operations. The only treatment available presently is symptomatic or possibly dialysis.[43]

Another important factor is to use the patient's absolute renal function and not the relative clearance the patient or subject would have had if his/her body surface area would have been 1.73 m^2 since most dose recommendations based on dose-effect studies use the absolute clearance.[34] "Absolute"= without correction for body surface area (mL/min) and "relative"= with correction for body surface area (mL/min/1.73m^2). In most patients, the difference between the two may be small but in certain patients, e.g. elderly women, in particular those with a body surface area (BSA) smaller than (the standard) 1.73 m^2, the difference may be considerable. A case report from France describes two elderly dabigatran-treated women 84 and 89 years old, respectively, one with a fatal and one with a serious hemorrhage. Plasma concentrations of dabigatran were reported to be high. Both patients had low weight, low relative creatinine clearance of 29 and 32 mL/min/1.73 m^2, respectively, and probably an absolute creatinine clearance below 30 ml/min, which is a contraindication for dabigatran treatment.[4]

For older remedies to prevent dangerously high doses in the elderly a comparison factor between older and newer methods to determine P-creatinine may be needed, however impractical. We found that the method used to estimate renal function has impact on recommended dabigatran doses in the elderly. Subsequently, one question remains to be answered; Can we rely on the measurements of renal function made in the initial dabigatran pharmacokinetic studies? This needs urgently to be elucidated for the elderly.

Elderly patients with decreased renal function are at particular risk for dose- and concentration-dependent ADRs. Their reduced renal function is not always noticed.[18] There is a great need of evidence-based support when prescribing drugs for elderly patients.[44] Before new methods to estimate renal function, e.g. MDRD4 and CKD-EPI, all being surrogate markers for renal function, are used for drug dosing in the elderly, the consequences must be well documented, including pharmacokinetic modeling and TDM (Therapeutic Drug Monitoring). In the most recent draft guideline from the US-FDA, both CG and MDRD4 may be used.[1] The current "Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function" from EMEA 2004 states that measuring GFR should be based on accurate well established methods (such as iohexol clearance).[45] In contrast to the US-FDA, there is no practical recommendation from EMA.

We support that recommended dabigatran dose-rate should be adjusted linearly for decreases in creatinine clearance and standard pharmacological principles.[46] We also suggest that the therapy in the elderly is more frequently guided by TDM, if available.

CONCLUSION

This data simulation study shows that the MDRD4 equation would result in higher doses of dabigatran, gabapentin, and valaciclovir to elderly subjects, particularly in women, compared to

the CG equation that was used during the clinical trials, and thus increase the risk of dose and concentration-dependent ADRs. Although dose recommendations for dabigatran in the SPC refer to both renal function and age, creatinine clearance according to CG is the basis for calculating recommended doses for dabigatran as for many other drugs with renal elimination. Doses based on other methods may be associated with considerable risk.

We are grateful to Maria Hentschke, RN, for her skilful contribution with the collection of patient data.

Contributions: AH, I O-C and UB initiated, designed and analysed the data and wrote the article.

GN, SS, AS, MvE, GÖ contributed with the collection and evaluation of patient data. All authors interpreted the data, critically revised the manuscript, and gave final approval of the version to be published. AH is the guarantor.

Funding: This study was supported by the Stockholm County Council (ALF 20060747, FOU project no. 560747) and by grants from the Karolinska Institutet.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES:

1. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. DRAFT GUIDANCE http://wwwfdagov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf 2010 (accessed 2012-02-03).
2. PRADAXA, EPAR. Summary for the public. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/medicines/human/medicines/000829/human_med_000981jsp&murl=menus/medicines/medicinesjsp&jsenabled=true (accessed 2012-10-28).
3. Casado Naranjo I, Portilla-Cuenca J, Jiménez Caballero P, Calle Escobar M, Romero Sevilla R. Fatal intracerebral hemorrhage associated with administration of recombinant tissue plasminogen activator in a stroke patient on treatment with dabigatran. Cerebrovasc Dis 2011;**32**:616-9. doi: 10.1159/000334578. Epub 2011 Dec 1.
4. Legrand M, Mateo J, Aribaud A et al. The use of dabigatran in elderly patients. Arch Intern Med 2011;**171**:1285-6. doi: 10.1001/archinternmed.2011.314.
5. Chen B, Viny A, Garlich F et al. Hemorrhagic complications associated with dabigatran use. Clin Toxicol 2012;**50**:854-7. doi: 10.3109/15563650.2012.721888. Epub 2012 Sep 12.
6. Food and Drug Administration. www.fda.gov/Drugs/DrugSafety/ucm282724.htm (accessed 12-02-03).
7. Ezekowitz MD, Reilly PA, Nehmiz G et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;**100**:1419-26. Epub 2007 Aug 17.

8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;**16**:31-41.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;**130**:461-70.
10. Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;**145**:247-54.
11. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;**150**:604-12.
12. Wuyts B, Bernard D, Van den Noortgate N et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. Clin Chem 2003;**49**:1011-4.
13. Chan MH, Ng KF, Szeto CC et al. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2004;**41**:482-4.
14. Delanghe J, Speeckaert M. Creatinine determination according to Jaffe- what does it stand for? NDT Plus 2011;**4**:83-6. doi: 10.1093/ndtplus/sfq211. Epub 2011 January 27
15. Nyman HA, Dowling TC, Hudson JQ, Peter WL, Joy MS, Nolin TD. 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. doi: 10.1592/phco.31.11.1130.
16. Gouin-Thibault I, Pautas E, Mahé I et al. Is Modification of Diet in Renal Disease formula similar to Cockcroft-Gault formula to assess renal function in elderly

hospitalized patients treated with low-molecular-weight heparin? J Gerontol A Biol Sci Med Sci 2007;**62**:1300-5.

17. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group--a cautionary tale. Nephrol Dial Transplant 2007;**22**:2894-9. Epub 2007 Jun 16.
18. Helldén A, Bergman U, von Euler M, Hentschke M, Odar-Cederlöf I, Öhlén G. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. Drugs Aging 2009;**26**:595-606. doi: 10.2165/11315790-000000000-00000.
19. Frank M, Guarino-Gubler S, Burnier M, Maillard M, Keller F, Gabutti L. Estimation of glomerular filtration rate in hospitalised patients: are we overestimating renal function? Swiss Med Wkly 2012;**142**:0. doi: 10.4414/smw.2012.13708.
20. Helldén A, Odar-Cederlöf I, Diener P et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant 2003;**18**:1135-41.
21. Söderström A, Bergman U, Helldén A, Odar-Cederlöf I. Renal function and drug treatment in a home care center in Farsta (Abstract. In Swedish). Poster LÄ 2P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.
22. Johansson M, Bergman U, Helldén A, Mejyr S, Öhlén G. Adverse drug reaction-related admissions at the Karolinska University Hospital, Huddinge- a follow up with focus on generic drug treatment. (Abstract. In Swedish) Poster AM25P at the General Meeting of the Swedish Society of Medicine, Gothenburg, Hygiea 2004.

23. Odar-Cederlöf I, Oskarsson P, Öhlén G et al. Adverse drug effect as cause of hospital admission. Common drugs are the major part according to the cross-sectional study (in Swedish). Läkartidningen 2008;**105**:890-3.

24. von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiol Drug Saf 2006;**15**:179-84.

25. Hedberg P, Lönnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. Eur Heart J 2001;**22**:676-83.

26. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010;**49**:259-68. doi: 10.2165/11318170-000000000-00000.

27. Levey AS, Coresh J, Greene T et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;**53**:766-72. Epub 2007 Mar 1.

28. Lamb EJ. Effect of a compensated Jaffe creatinine method on the estimation of glomerular filtration rate. Ann Clin Biochem 2005;**42**:160-1.

29. Dabigatran (Pradaxa): risk of bleeding relating to use. (www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm) (Accessed 2012-01-10).

30. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. Ann Pharmacother 2012;**46**:e10. doi: 10.1345/aph.1Q747. Epub 2012 Apr 10.

31. Denetclaw TH, Oshima N, Dowling TC. Dofetilide dose calculation errors in elderly associated with use of the modification of diet in renal disease equation. Ann Pharmacother 2011;**45**:e44 doi: 10.1345/aph.1Q159. Epub 2011 Jun 28.

32. Stevens L, Nolin T, Richardson M et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;**54**:33-42. 2009 Jul;54(1):33-42. doi: 10.1053/j.ajkd.2009.03.008. Epub 2009 May 17.

33. Wargo K, Eiland E3, Hamm W, English T, Phillippe H. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother 2006;**40**:1248-53. Epub 2006 Jul 11.

34. Spruill WJ, Wade WE, Cobb HH. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009;**86**:468-70. doi: 10.1038/clpt.2009.187.

35. Hermsen E, Maiefski M, Florescu M, Qiu F, Rupp M. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy 2009;**29**:649-55. doi: 10.1592/phco.29.6.649.

36. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134763.pdf (accessed 12-03-20).

37. Dabigatran S. http://www.medicines.org.uk/emc/medicine/20760/SPC/ (accessed 12-03-13).

38. Pradaxa EPAR- Product information. http://wwwemaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf (accessed 2012-03-13)

39. Eriksson BI, Dahl OE, Ahnfelt L et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. J Thromb Haemost 2004;**2**:1573-80.

40. Trocóniz I, Tillmann C, Liesenfeld K, Schäfer H, Stangier J. Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. J Clin Pharmacol 2007;**47**:371-82.

41. Lehr T, Haertter S, Liesenfeld KH et al. Dabigatran Etexilate in Atrial Fibrillation Patients with Severe Renal Impairment: Dose Identification Using Pharmacokinetic Modeling and Simulation. J Clin Pharmacol 2012;**52**:1373-8. doi: 10.1177/0091270011417716. Epub 2011 Sep 28.

42. Charhon N, Neely MN, Bourguignon L, Maire P, Jelliffe RW, Goutelle S. Comparison of Four Renal Function Estimation Equations for Pharmacokinetic Modeling of Gentamicin in Geriatric Patients Antimicrob Agents Chemother 2012;**56**:1862-9. doi: 10.1128/AAC.05634-11. Epub 2012 Jan 30.

43. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. N Engl J Med 2011;**365**:2039-40. doi: 10.1056/NEJMc1111095.

44. Tawadrous D, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis 2011;**58**:903-14. doi: 10.1053/j.ajkd.2011.07.022. Epub 2011 Sep 23.

45. Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf (Accessed 2013-01-31)

46. Chin PK, Vella-Brincat JW, Barclay ML, Begg EJ. Perspective on dabigatran etexilate dosing - why not follow standard pharmacological principles? Br J Clin Pharmacol 2012;74:734-40. doi: 10.1111/j.1365-2125.2012.04266.x.

LEGENDS .

Figure 1. Renal function estimated in 790 individuals aged 65 and older by the Cockcroft & Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in mL/min) and MDRD4 calculated according to the equations in Table II. Estimated GFR (eGFR) is given as a relative value (mL/min/1.73m^2). Mean ± SEM. Uncompensated creatinine denotes S/P-creatinine determined with the "old Jaffe" analysis.(13)

Figure 2 a-c. Data simulation of recommended daily doses for dabigatran (Figure 2 a), valaciclovir (Figure 2 b) and gabapentin (Figure 2 c) in relation to renal function by the Cockcroft-Gault formula (green staples) and the abbreviated Modification of Diet in Renal Disease (MDRD4) formula (red staples) in 790 subjects 65 years and older in Sweden. Dose recommendations by the MDRD4 formula will result in significantly higher doses, particularly in women. As an example, 19% (82) of the female subjects would receive an ordinary dose (300 mg) of dabigatran if the Cockcroft & Gault equation with uncompensated P-creatinine would be used when estimating renal function, compared to 59% (259) with the MDRD4 formula (Figure 2 a). Recommended daily dose for gabapentin is in general in a range from e.g. 900 - 3600 mg if creatinine clearance is higher than 80 mL/min. We have chosen to show half of the maximum recommended dose in each *stratum*.

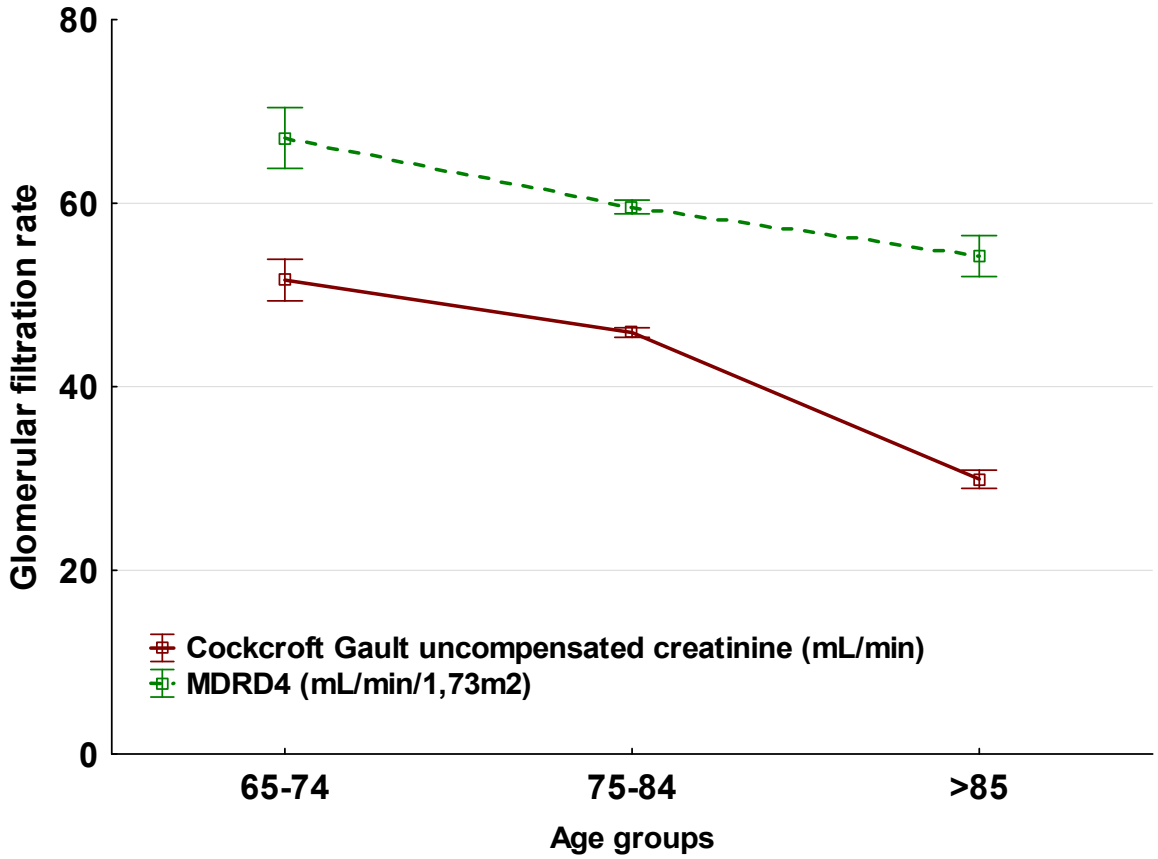

Figure 1.

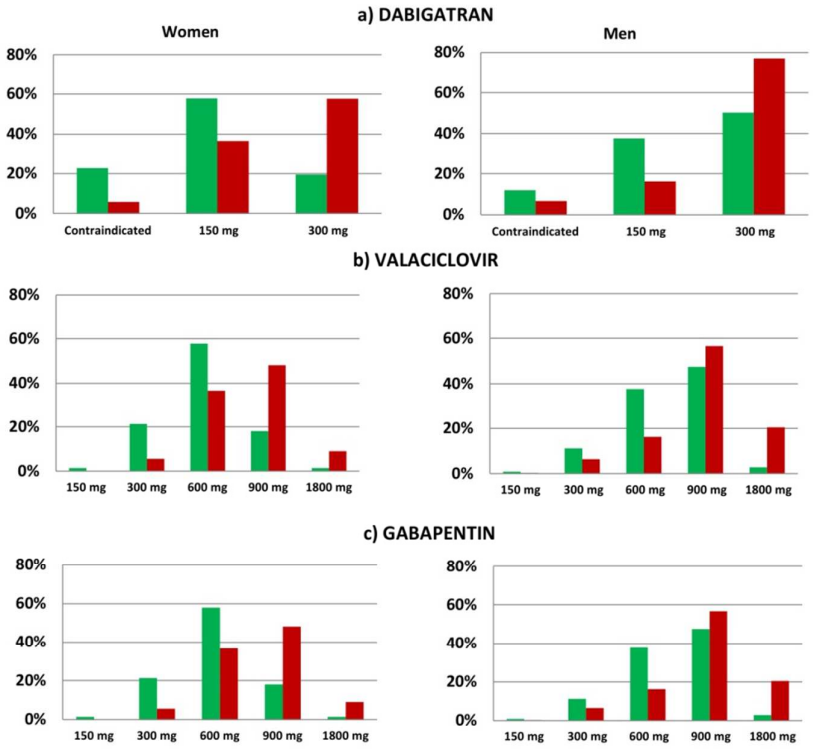

Figure 2 a-c)

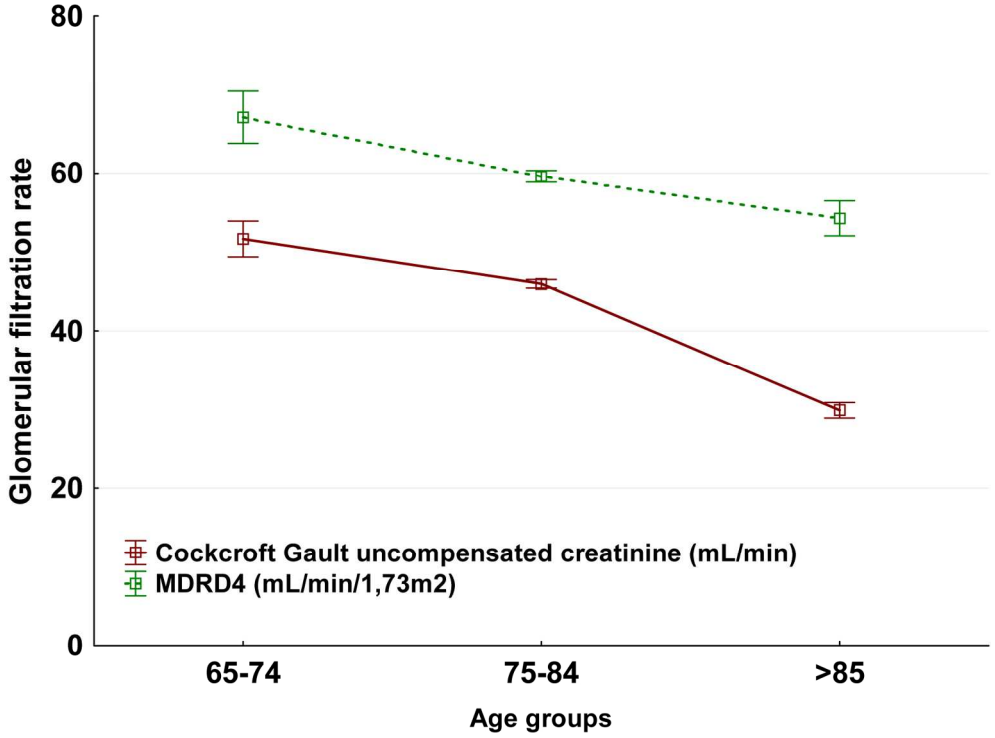

Figure 1. Renal function estimated in 790 individuals aged 65 and older by the Cockcroft & Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in mL/min) and MDRD4 calculated according to the equations in Table II. Estimated GFR (eGFR) is given as a relative value (mL/min/1.73m2). Mean ± SEM. Uncompensated creatinine denotes S/P-creatinine determined with the "old Jaffe" analysis.(13)

165x124mm (300 x 300 DPI)

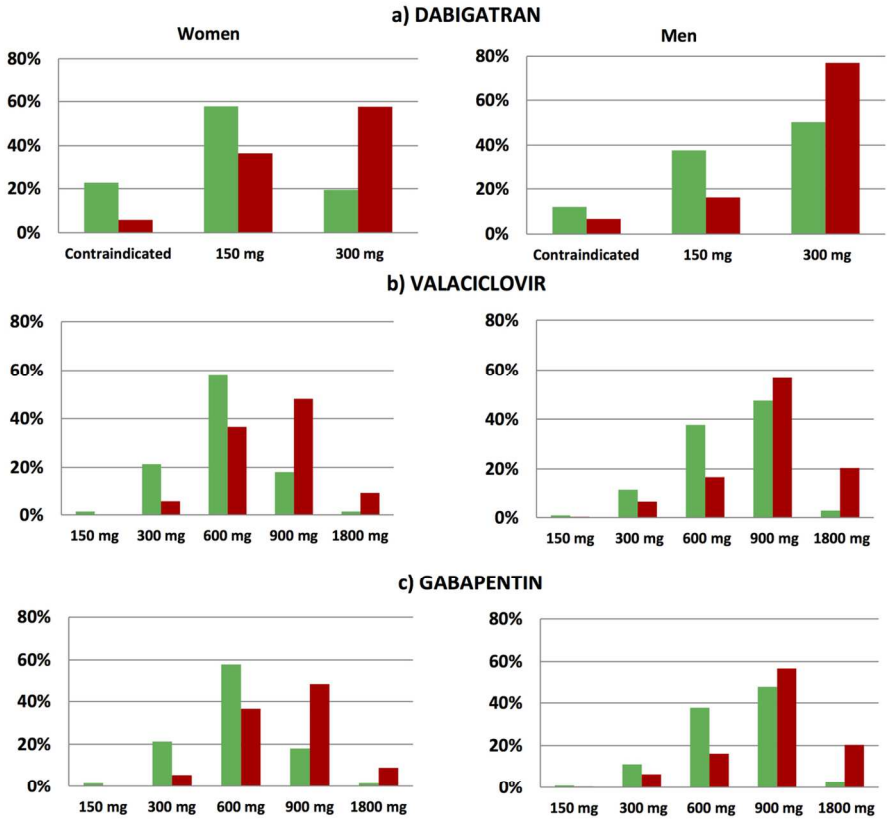

Figure 2 a-c. Data simulation of recommended daily doses for dabigatran (Figure 2 a), valaciclovir (Figure 2 b) and gabapentin (Figure 2 c) in relation to renal function by the Cockcroft-Gault formula (green staples) and the abbreviated Modification of Diet in Renal Disease (MDRD4) formula (red staples) in 790 subjects 65 years and older in Sweden. Dose recommendations by the MDRD4 formula will result in significantly higher doses, particularly in women. As an example, 19% (82) of the female subjects would receive an ordinary dose (300 mg) of dabigatran if the Cockcroft & Gault equation with uncompensated P-creatinine would be used when estimating renal function, compared to 59% (259) with the MDRD4 formula (Figure 2 a). Recommended daily dose for gabapentin is in general in a range from e.g. 900 - 3600 mg if creatinine clearance is higher than 80 mL/min. We have chosen to show half of the maximum recommended dose in each stratum.

128x117mm (300 x 300 DPI)