PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir. A data simulation study focusing on the elderly.
AUTHORS	Helldén, Anders; Odar-Cederlöf, Ingegerd; Nilsson, Goran; Sjöviker, Susanne; Söderström, Anders; von Euler, Mia; Öhlén, Gunnar; Bergman, Ulf

VERSION 1 - REVIEW

REVIEWER	O'Callaghan, Chris University of Oxford UK
REVIEW RETURNED	29-Apr-2012

GENERAL COMMENTS	This paper is composed of two simple parts. Firstly, there is a comparison of the values for estimated glomerular filtration rate (eGFR) that are produced by the MDRD, CKD-EPI and Cockcroft-Gault formulae for a sample of patients. Secondly, there is a prediction of the dose of a drug that would be prescribed based on these different GFR-predicting formulae. The drug chosen is the oral anti-coagulant dabigatran but the patients are not on this drug. Considering the first part – It is well known and well reported that different formulae produce different estimates of glomerular filtration rate. There are many papers reporting these differences and many papers documenting the extent to which these formulate do or do not correlate with true measured glomerular filtration rate. Some of these previous studies have used sample sizes two to three orders of magnitude larger and covered unselected patient populations including the elderly. This first part of the paper does not yield any substantial new insight beyond what is already known. Considering the second part – The manuscript does not contain any clinical data on the use of dabigatran in patients with renal impairment. Instead, what is presented is, in essence, a simple tabulation of the dose that would be administered to people based on current prescribing advice using each of the estimates of glomerular filtration rate derived from the

	different formulae in part one of the study. Given that we already know that different formulae produce somewhat different estimates of glomerular filtration rate, clearly there will be differences in the dosing advice for patients. This follows automatically as there will be patients for whom a different formula pushes them across a prescribing threshold. In this case, the threshold of interest was that of an eGFR of 50ml/min/1.73m2. Inevitably there were patients who were moved across this threshold in one direction or another by the use of different formulae. For any drug that is principally excreted by the kidneys, it is well known that dose changes will be required for different levels of renal dysfunction; hence the advice in formularies such as the British National Formulary about dose changes with renal function. Issues relating to renal function and the dabigatran has been widely publicised and have been the subject of notices from medicine regulatory authorities relatively recently, so doctors are aware of this. Given this, the second part does not yield any substantial insight that was not already known. Overall conclusions In essence, what is reported follows necessarily from the fact that the different formulae produce different glomerular filtration rate predictions and that dabigatran, like various other drugs will accumulate with renal dysfunction. In most countries the MDRD formula is used for routine eglomerular filtration rate reporting as a matter of national policy. Unlike the Cockcroft-Gault formula it does not require measurement of weight and so can be reported directly by biochemistry laboratories. However, the CKD-EPI formula is likely to replace the MDRD formula as it has a better correlation with true measured glomerular filtration rate. The Cockcroft-Gault formulae is not commonly used now. It has been well appreciated that simultaneous use of several formulae will lead to confusion; it is precisely for this reason that national and international guidelines have been established to promote the use of one equation with calibration controls to standardise the results across laboratories. An issue that is recognised is that historical drug safety data has been collected using various different approaches to assess renal function including direct measurement of creatinine clearance, or eGFRs derived from the Cockcroft-Gault formula or other formulae such as the MDRD equation. This issue was a factor discussed and taken into account in 2009 by the BNF when it altered its prescribing advice for renal impairment to the use MDRD-based eGFR results rather than creatinine clearance which it had previously used. Increasingly drug safety data is being collected using eGFRs calculated with the MDRD or CKD-EPI formulae. As both the MDRD and CKD-EPI formulae use the same input variable of blood creatinine, age, sex and ethnicity, safety data based on MDRD can be easily updated to base it on CKD-EPI.

	Ultimately no routine method of estimating glomerular filtration rate is perfect and there is no substitute for therapeutic drug monitoring where there is doubt; even if glomerular filtration rate is known precisely, there remain other variables such as absorption and compliance/concordance with prescribed dosing. The study does not demonstrate whether any of the changes discussed would actually cause problems for patients. The cut off levels for prescribing advice are relatively arbitrary and a small shift across a borderline from 49 to 51 ml/min/1.73m2 may alter the advice given, but may be of limited clinical significance. This remains to be established in an experimental study. What would be interesting is a study of drug levels in a series of patients with different levels of renal function as calculated with the formula that is to be used in the community in consideration. In conclusions, my view is that this study does not have sufficient novelty or scientific value to merit publication in the BMJ.

REVIEWER	MacDonald, Thomas University of Dundee, Division of Medical Sciences
REVIEW RETURNED	03-May-2012

GENERAL COMMENTS	This paper reports on the variation between differing methods of reporting GFR estimations which is not in itself new data. What is new is the fact that these data are in elderly subjects a population in which the differences between methods appears exaggerated. Data has been retrieved on 790 subjects (from studies previously published). Unfortunately, no gold-standard GFR measure such as Cr51 or inulin clearance has been done. The paper applies these various GFR data to the theoretical use of dabigatran and concluded that the use of the 'wrong' GFR measure will result in less safe prescribing. Whilst the big differences in GFR estimations in elderly patients is of interest to clinicians, the present paper does not offer a solution as to how to deal with this other than to always use the same measure as the SPC. This is not always practical. The data in the paper might be of greater value if the authors could produce a 'translation table' between Cockroft Gault (CG) and MDRD levels of GFR by age group and possibly sex. Fig 1 suggests that this might be possible? This might allow the SPC for a drug, which usually uses CG to be translated by age into MDRD and provide a generic mapping. I am not sure if this has been done before but my clinical chemistry colleagues could not think of such data. This does appear to be a ‘fixable’ issue in improving the risk-management of medicines in general. Maybe labs could include height and weight and calculate CG if requested? The message that the method matters is currently drummed into pharmacists and clinical chemists but to a lesser extent to junior doctors so this in itself is not novel. However, the major variation between MDRD (the eGFR reported by most labs) and CG (the measure used when developing medicines) does seem worthy of more publicity.

	The link to dabigatran is theoretical and no data are presented on actual cases. These GFR data might just as easily be applied to other drugs excreted mainly by the renal route. Perhaps some other drugs could be modelled? Whilst I understand that dabigatran may have been the stimulus for this paper, this theoretical 'explanation' for dabigatran SAEs might be inappropriately used by the manufacturer to deflect blame for dabigatran SAEs away from the drug to the prescribing physician. Whilst this might be appropriate, no data are presented that renal function measures are actually the explanation for dabigatran SAEs at present. I am keen therefore that the paper does NOT focus on dabigatran. However, perhaps the application to dabigatran might constitute a 'lessen of the week'? I have heard one of the authors present these data at the European Medicines Agency and I am aware that there are also survey data from hospital labs comparing methodologies. These data would add to the utility of this paper (suitably anonymised). The paper requires significant sub-editing to improve its readability and focus. In particular the six page discussion needs trimmed.

- The manuscript received a second and third review at the BMJ but the reviewer did not give permission for their comments to be published

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation:

Comments:
This paper is composed of two simple parts.

Firstly, there is a comparison of the values for estimated glomerular filtration rate (eGFR) that are produced by the MDRD, CKD-EPI and Cockcroft-Gault formulae for a sample of patients.

Secondly, there is a prediction of the dose of a drug that would be prescribed based on these different GFR-predicting formulae. The drug chosen is the oral anti-coagulant dabigatran but the patients are not on this drug.

Considering the first part –

It is well known and well reported that different formulae produce different estimates of glomerular filtration rate. There are many papers reporting these differences and many papers documenting the extent to which these formulate do or do not correlate with true measured glomerular filtration rate. Some of these previous studies have used sample sizes two to three orders of magnitude larger and covered unselected patient populations including the elderly. **This is correct, but it does not take drug dosing into account. However, a recently published review on estimation formulas in the elderly including more than 11000 subjects clearly shows that the MDRD formula results in 15 – 20 mL/min higher clearance compared to the CG formula. In our simulation study, where the difference approached 30 ml/min, we show that these differences clearly increase dose**

recommendations in the elderly.

This first part of the paper does not yield any substantial new insight beyond what is already known. **It might be known, but is it implemented? At a meeting last autumn with a group of UK nephrologists, they were not aware of the difference between the methods in the very old and urged AH to publish the results.**

Considering the second part –

The manuscript does not contain any clinical data on the use of dabigatran in patients with renal impairment. Instead, what is presented is, in essence, a simple tabulation of the dose that would be administered to people based on current prescribing advice using each of the estimates of glomerular filtration rate derived from the different formulae in part one of the study.

Given that we already know that different formulae produce somewhat different estimates of glomerular filtration rate, clearly there will be differences in the dosing advice for patients. This follows automatically as there will be patients for whom a different formula pushes them across a prescribing threshold. In this case, the threshold of interest was that of an eGFR of 50ml/min/1.73m2. Inevitably there were patients who were moved across this threshold in one direction or another by the use of different formulae. **In fact, 50% of the studied subjects moved up one (45%) or two (5%) CKD stages, while only 2% moved in the other direction.**

For any drug that is principally excreted by the kidneys, it is well known that dose changes will be required for different levels of renal dysfunction; hence the advice in formularies such as the British National Formulary about dose changes with renal function.

Issues relating to renal function and the dabigatran has been widely publicised and have been the subject of notices from medicine regulatory authorities relatively recently, so doctors are aware of this.

Given this, the second part does not yield any substantial insight that was not already known.

Overall conclusions

In essence, what is reported follows necessarily from the fact that the different formulae produce different glomerular filtration rate predictions and that dabigatran, like various other drugs will accumulate with renal dysfunction.

In most countries the MDRD formula is used for routine eglomerular filtration rate reporting as a matter of national policy. Unlike the Cockcroft-Gault formula it does not require measurement of weight and so can be reported directly by biochemistry laboratories. However, the CKD-EPI formula is likely to replace the MDRD formula as it has a better correlation with true measured glomerular filtration rate. The Cockcroft-Gault formulae is not commonly used now.

It has been well appreciated that simultaneous use of several formulae will lead to confusion; it is precisely for this reason that national and international guidelines have been established to promote the use of one equation with calibration controls to standardise the results across laboratories.

An issue that is recognised is that historical drug safety data has been collected using various different approaches to assess renal function including direct measurement of creatinine clearance, or eGFRs derived from the Cockcroft-Gault formula or other formulae such as the MDRD equation. This issue was a factor discussed and taken into account in 2009 by the BNF when it altered its prescribing advice for renal impairment to the use MDRD-based eGFR results rather than creatinine clearance which it had previously used. Increasingly drug safety data is being collected using eGFRs calculated with the MDRD or CKD-EPI formulae. As both the MDRD and CKD-EPI formulae use the same input variable of blood creatinine, age, sex and ethnicity, safety data based on MDRD can be easily updated to base it on CKD-EPI. **We still cannot see the rational in a drug recommendation based on the MDRD4 formula that results in a full dose of e.g. valaciclovir to a 90-year-old woman compared to 1/3 of the dose if CG is used. In addition, we show that 55% of our cohort**

will receive higher doses of gabapentin.

Ultimately no routine method of estimating glomerular filtration rate is perfect and there is no substitute for therapeutic drug monitoring where there is doubt; even if glomerular filtration rate is known precisely, there remain other variables such as absorption and compliance/concordance with prescribed dosing.

The study does not demonstrate whether any of the changes discussed would actually cause problems for patients. The cut off levels for prescribing advice are relatively arbitrary and a small shift across a borderline from 49 to 51 ml/min/1.73m2 may alter the advice given, but may be of limited clinical significance. This remains to be established in an experimental study.

What would be interesting is a study of drug levels in a series of patients with different levels of renal function as calculated with the formula that is to be used in the community in consideration.

In conclusions, my view is that this study does not have sufficient novelty or scientific value to merit publication in the BMJ.

Additional Questions:
Please enter your name: Chris O'Callaghan

Job Title: Professor of Medicine, Hon Consultant Nephologist and General Physician

Institution: University of Oxford, Oxford University Hospital Trust

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (either as indicated above or any other financial or non-financial interests) please declare them here: I receive grant funding from the Medical Research Council, the Wellcome Trust, the British Heart Foundation and the British Renal Society. These are either government agencies (MRC) or medical charities and receipt of these funds does not constitute a conflict of interest that I perceive, but I am declaring them for transparency.

VERSION 2 – REVIEW

REVIEWER	C.A O'Callaghan DPhil DM FRCP Professor of Medicine Hon Consultant Nephrologist and General Physician Nuffield Department of Medicine University of Oxford
REVIEW RETURNED	10-Feb-2013

THE STUDY	The title is somewhat alarmist and there is no evidence of danger in the data presented.
GENERAL COMMENTS	This manuscript presents a study in which a set of creatinine values from six previously published studies of elderly patients were used to estimate glomerular filtration rate (GFR) using both the Cockcroft-Gault formula and the MDRD formula. There is already good evidence that these two formulae produce different estimates of GFR and that the MDRD formula produces a more accurate estimate of true measured GFR than the Cockcroft-Gault formula (eg. Michels et al. 2010, Clin J Am Soc Nephrol 5: 1003–1009). The group that produced the MDRD formula have now developed the CKD-EPI formula which produces even better estimates of measured GFR and is being used increasingly in research and clinical practice. The authors then use the estimated GFRs (eGFRs) to decide what dose of a drug each patient would receive based on suggested dose adjustments for renal impairment. It follows logically from the known difference between eGFRs calculated with the two formulae that there will necessarily be differences between the recommended doses for some patients. This is what the authors observe in this simulation exercise using dosing guidelines for dabigatran, valaciclovir and gapapentin. The use of the word ‘dangerous’ in the title might be considered somewhat alarmist given that there is no evidence of danger in the data presented and some qualifications need to be borne in mind when interpreting the findings presented. The authors underlying argument is that historically the MDRD formula was not used to develop drug dosing recommendations and so should not be used as a basis for determining dosing for individual patients. Drug dosing recommendations have often been based on the Cockcroft-Gault formula or measured creatinine clearance. Creatinine clearance is inherently unreliable due to the error associated with incomplete 24 hour urine collection. It is possible that in the drug trial situation, there may be less error associated with the collection, but quantification of any such error is problematic. In practice, the MDRD formula produces a more accurate estimate of true GFR than is obtained by measuring creatinine clearance and creatinine clearances have ceased to be used in most contexts. It is difficult to argue that it is preferable to use less accurate estimates of renal function such as those produced by the Cockcroft-Gault formula or creatinine clearance rather than the more accurate estimate produced by the MDRD formula. Glomerular filtration rate has a continuous rather than a categorical distribution within the population. The categorisation of patients into groups based on estimates of GFR may be contributing to some

	over interpretation of the data. It must be remembered that those patients who would have a different drug dose depending on which formula was used to estimate their GFR are likely to be those close to the boundary between the different eGFR categories. Thus, if a patient's eGFR moves from just below 50 with the Cockcroft-Gault formula to just over 50 with the MDRD formula their recommended dose will be increased, but is there really any meaningful difference in renal function between patients close to either side of the arbitrary 50 ml/min/1.73m2 cut off. Whilst it is often helpful for guidelines to stipulate renal function cut off boundaries for drug dosing, it is important not to overestimate the meaning of the boundary itself. Thus, although the doses may alter depending on which formula is used to calculate eGFR, this does not mean that the doses are dangerous. The authors do not provide any demonstration of elevated drug levels in any of the patients studied, so ultimately no firm conclusions about safety can be made.

VERSION 2 – AUTHOR RESPONSE

1. In our study, we cited the evidence showing the GFR differences between the Cockcroft & Gault formula (CG) and the MDRD formula. However, our main objective was to show if these differences had an impact on the potential dosing, rather than just showing that they exist. We found those differences particularly evident in the elderly.

2. We have rephrased the initial words in the title to "Potentially dangerous".

3. We regret to say we do not have clinical data, such as drug levels, from this simulation study. However, such data are by now well documented in many reports, some of which are also referred to in our manuscript.

4. In November 2011, a Dear Health Care Professional letter was published, and in this it is clearly stated that drug dosing with dabigatran has to be done with a formula including weight. This is not part of the methods referred to by the referee. The suggested method is indeed the CG formula.

5. Furthermore, the referee has not commented upon the difference in absolute vs relative values of GFR, i.e. related to body surface area (BSA). The former has been used in almost all pharmacokinetic studies as the basis for dose recommendations. It has been shown that the relative values become more and more uncertain in the elderly, particular in elderly women, and cannot be used for dose recommendations. In a paper by Stevens et al, referred to in our article (reference no 32), the authors state that MDRD can be used for drug dosing. However, in the paper the MDRD formula was individualized for BSA and expressed in mL/min. Thus, the advantage of expressing MDRD (in mL/min/1.73m2) in the clinic is diminished by the need of height when the formula is used for drug dosing.

6. We are aware of the fact that there may be better methods to estimate renal function than the Cockcroft Gault (CG) equation. We have by now many years of experience of CG in pharmacotherapy, and basically most SPC texts about renal function are based on this equation. Future reliance on newer equations may get into act, but caution should be taken when dosing medications based on those equations.

It is worth mentioning that two of the three of us taking the initiative to this study, are also specialists in Nephrology. We are therefore well aware of the pros and cons with the old and new methods of estimating renal function. However, we are also specialists in Clinical Pharmacology, and with this combined background we have encountered significant problems with the new methods in the elderly, and particularly in women.

Finally, our paper highlights a potential problem that might have serious consequences for certain elderly subjects, and should as such be discussed in the scientific community.