Dear Dr. Silver,

Manuscript ID BMJ.2015.027294 entitled "Risk Prediction Models for Contrast Induced Nephropathy: A Systematic Review"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. We recognise its potential importance and relevance to general medical readers, and hope we will be able to accept it once you have revised it to clarify several important aspects of the work and respond to reviewers' comments.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript committee meeting.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a final decision.

**THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS’ REPORTS, AND THE BMJ’S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

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Very truly yours,

Elizabeth Loder, MD, MPH
BMJ Editorial Team
As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation ‘Revised Manuscript Marked copy’.

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INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: xxx (chair), yyy (statistician), [and list other eds who took part]

Decision: request revisions

RQ: presumably high value
Reviews: moderate value
Merit: moderate ?high

Observations:
- quite a critical look at these prediction tools
- the authors are not impressed by the predictive ability of these tools as a whole, but refrain from looking at the best of the bunch, as the reviewers point out
- given that there all derived from different cohorts and have different variables I really i am not surprised by the heterogeneity they found
- the C statistics are on average, moderate, and in some cases (the Victor study) look quite good indeed (c/f Framingham, QRISK2 etc)
- what’s missing is a clinical look at the utility of these tools, not unlike our discussion at last weeks MM about pre-eclampsia tools
- are these tools used in coronary angiography? what are the implications of being scored as high risk in terms of prevention

- the paper needs a bit of tightening up, the authors could loosen up a little and try and take some positives from their work, and if accepted might work well with other risk tools with an overview from some of the risk prediction methods folks from Utrecht

PreMM Tiago
Updated By: Villanueva Tiago - Editor on 01-Jul-2015

This is all new to me, but enjoyed reading this paper, which seems like the start of an interesting story. It would have been nice to have an idea if these risk prediction tools are actually used widely or not in clinical practice, since they’ve been around for 10 years, which is too much time for these tools to have been used inappropriately. Because the review only included trials where contrast was administered for a coronary procedure, these risk prediction models won’t be relevant, for example, for the increasingly frequent neuro-radiological procedures.

I am supportive. This might make a nice pair with that umbrella review on risk prediction models for pulmonary embolism which we discussed a few weeks ago (I thin the decision was put points).

Possible companion paper: 26658 Risk of post-operative AKI in patients undergoing orthopaedic surger
Updated By: Weber Wim - Editor on 02-Jul-2015

PP at MM 18 June 2015

preMM WW
Updated By: Weber Wim - Editor on 02-Jul-2015

It seems well done, but they were obviously limited by the studies they had to work with. The conclusion that ‘more research is needed’, is probably true, and I initially wondered if that is enough for us?

But their cover letter is quite persuasive; it is a topic that affects many disciplines as almost all will order these investigations, and this now shows that we cannot predict who will be affected.

There are 64 papers with 'Contrast Induced Nephropathy' in the title with > 64 citations

Pre MM RB
Updated By: Burch Rebecca - Research Committee on 02-Jul-2015

I agree with the concerns about clinical usefulness that Busch raised. In the real world some kind of prediction has to be used, and while it’s helpful to know that more work needs to be done I found myself wondering how helpful this was for current practice.

From looking through table 3, the prediction score that looks the best is Maoli, which was externally validated in a separate cohort (different institution? unclear) and performed fairly well. Could the authors
do more to recommend what to do now? Otherwise I’m not sure this is enough for us.

Pre MM AT
Updated By: Tonks Alison - Editor on 02-Jul-2015

Just for once I can see the point of these prediction models. Patients at high risk could opt out of the investigation, try other investigations, or use risk reduction strategies (limited I know). So in principle I’m in favour of paper synthesising the evidence underpinning these models, even if the final conclusion is “more work required”.

The paper reads well and maintained by interest. As others have said, the authors could do a better job comparing and contrasting the real value of these models in clinical situations. Which ones look better validated? better performing? Should future researchers build on those and discard the others?

They could also point researchers where to go next. Top of the list would be prospective “trials” to see if using any of the better performing models actually improved patient outcomes. This final step is often missing in prediction modelling, and the authors should emphasise the need for this kind of evaluation. Without it, developing models is a dry statistical exercise that may or may not actually help patients.

Currently, their definition of clinical utility is very broad. A model had utility if the authors discussed how it might help decision making. Surely just a measure of the authors own faith in their model.

Stats-MM
Updated By: Perera Rafael - Research Committee on 02-Jul-2015

This paper is asking a relevant question summarising the evidence on the prediction rules available for CIN. I would have liked to see some figures summarising the data but in principle there is not much wrong with the article.

There is an issue as to how these results could be made more useful. It could be through specific recommendations on which models appear to have the most potential stratified by setting. This would certainly add novelty to the manuscript.

Report of the manuscript meeting of 2 July 2015
Updated By: Loder Elisabeth - Research Committee on 02-Jul-2015

Present: Elizabeth Loder (chair); Rafael Perera (statistician); Wim Weber; Rebecca Burch; Rubin Minhas; Tiago Villanueva; Alison Tonks

Decision: Put points. Statistician will review the revision once it is returned.

* We were pleased to see this complex review that tries to integrate evidence while taking account of the variability of populations and other factors. We felt that in general you had done a very good job of this. We agreed with reviewers that it would be helpful to put the findings in more clinical context. For example, might you say which of the models is the most likely candidate for further development? Might you comment on how the C statistic and performance of some of these models compare to other risk prediction models (in other therapeutic areas) that are in clinical use despite not being perfect?

* We also wondered whether some results and findings might be presented graphically, since this sort of visual presentation is often very interesting for readers.

* Can you examine or speculate about the source(s) of heterogeneity? Many of these models seem to have been evaluated in the setting of coronary angiography, so is it the case that their utility should be examined more narrowly, in particular patients or populations? You might say more about how they perform in the predominant situations in which they are used.

* Since existing models do not perform well, we thought it would be useful to expand your discussion of what the next generation of research should look like. For example, do we need a trial showing whether using these models changes patient outcomes?

*The above are all suggestions and if any seem beyond the scope of your paper or do not make sense to you, please feel free to simply say that in response!

* Please also respond to reviewer comments and suggestions.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg “systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sAMPL/summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used.

For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system

Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic. Please follow this structure:

statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews) meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors.

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a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:

did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)

was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)

were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)

have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)

are patients thanked in the contributorship statement or acknowledgements?

for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
Silver S. et al. have performed a systematic review with the title "Risk Prediction Models for Contrast Induced Nephropathy: A Systematic Review". The manuscript aimed to systematically review prediction models of contrast induced nephropathy (CIN). A total of 16 studies describing 12 prediction models of CIN were included. All 12 models were validated internally or externally using c-statistics. All models were developed and validated in a population undergoing coronary angiography and/or percutaneous coronary intervention. The authors found that the models were heterogeneous regarding the included variables and the external validation showed that their ability for predicting CIN varied markedly between studies.

The manuscript address an important clinical problem since CIN is a common cause of acute kidney injury. No clinical model for predicting CIN is universally recommended. Moreover, no preventive strategy besides hydration has been shown to be effective.

The manuscript is original, adheres to the PRISMA guidelines, well designed and the first attempt to unite the knowledge on different predictive models of CIN. The manuscript is well written and the abstract reflects accurately the content of the manuscript. The challenge of CIN and knowledge of predictive models is relevant to a wide range of medical specialties and for many clinicians. CIN is not only a challenge after intracoronary contrast administration but also occurs in relation to e.g. CT-scans with iv contrast. Therefore, a general journal could be the right place for this publication.

The manuscript has a clearly defined research question. However, it is in the main text answered in too general terms. A more precise presentation of each model would be preferred in the result section as a part of the main text and not just in table and appendix table format. Moreover, a thorough discussion of each model is missing. Is one model better validated than other? What could be the reason for differences in c-statistics for the models validated in more than one study? What are the precise differences between the models? The authors use general terms such as "heterogeneity in patient populations and clinical scenarios" (page 15 line 13). Could one model potentially be recommended for clinical use since no good alternatives exist at the moment? What should the clinician consider when making a decision in practice?

Minor comments
1) Page 11, line 10: Variables such as age, DM, and contrast volume is included in the majority of the models. Please include this.
2) Table 2: Add number of patients included in each study
3) Table 3: In the part "derivative cohort" a column with "number of included patients" and "population" would provide a better overview for the reader.
4) Table 4: The authors should consider not including "clinical usefulness" in a judgment of risk of bias. In general the table in hard to understand and does not with the current layout add anything useful to the manuscript.
5) Please discuss whether it is at all possible to develop a predictive model of CIN which can be used in different clinical settings and populations. How should we design future studies when aiming to develop a potentially robust model for predicting CIN?
6) Reference 2 (McCullough PA et al 1997) and 3 (Nash K et al. 2002): Please consider substituting with more up-to-date references.

The manuscript could be accepted with major revision.

Additional Questions:
Please enter your name: Sarah Victoria Ekeloef Busch
Job Title: MD, Ph.D. student
Institution: Center for Surgical Science, Department of Surgery, Koeg Hospital, Denmark
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
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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 (please see BMJ policy) please declare them here:

Reviewer: 2
Recommendation:
Comments:
Silver et al. performed a systematic review of papers published on the topic of risk prediction models for contrast-induced nephropathy (CIN). By definition, systematic reviews involve a detailed and comprehensive plan and search strategy derived a priori. Using this approach bias is reduced by identifying, appraising, synthesizing, and if possible analysing all relevant studies. The selection process in this paper is clearly explained and depicted in Figure 1 and in Supplemental Appendix 1. However, on page 10 in the first Results-section 3509 citations were excluded by screening of title and abstract. Please state the main reasons for exclusions. In a next step 42 studies were excluded, I guess this time after full text evaluation, please include information in a sentence or two why these studies did not fulfill the inclusion criteria.

More than 70,000 patients were included in the review, and the incidence of CIN was 4%. This is not only the first systematic review on this topic, but the patient numbers should be also high enough to draw conclusions for daily clinical practice (if possible).

Statistics: model-performance was calculated and c-statistic was used a as a measure of discrimination. The results are nicely summarized in Table 3. The authors state that they assessed study quality (=bias, Table 4) using a modification of criteria recommended by Hayden et al, Ann Intern Med 2006, and also that they assessed clinical usefulness of the prediction models as suggested by Tangri et al, Ann Intern Med 2013. Despite these references it is not clear to the reader how the authors conclude the size of bias in Table 4 (low, high, ?), it seems somehow arbitrary, which is in contrast to a "systematic" review. Please clarify and extend this paragraph and also Table 4, so that the reader can follow your rationale.

Further, in Table 4 nine of twelve risk predictors are termed "clinically useful" which is in sharp contrast to the Discussion section, in which the authors explain all the (correct) limitations of the studies. This is puzzling and contradictory, please clarify and include in the Discussion section.

Finally, the authors correctly state that this systematic review illustrates the heterogeneity of the studies per se, and particularly of discovery and validation cohorts. This is a very valuable finding in particular because all of these studies evaluated risk prediction in the same setting: coronary angiography and PCI. No intravenous CT scans! When risk prediction models perform so poorly in studies evaluating the same intervention, how can we be able to define risk prediction models for CIN in general (PCI, peripheral angiography, venous for CT, venous PTA, etc...)?

Additional Questions:
Please enter your name: Michael Rudnicki

Job Title: MD
Institution: Medical University Innsbruck
Reimbursement for attending a symposium?: Yes
A fee for speaking?: Yes
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Date Sent: 03-Jul-2015