BMJ - Decision on Manuscript ID BMJ.2014.024391

Body: 26-Feb-2015

Dear Dr. Chung

Manuscript ID BMJ.2014.024391 entitled "Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and the United Kingdom"

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, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. Looking forward to hearing from you again and, we hope, to reaching a decision.

Deadline: Your revised manuscript should be submitted within 6 to 8 weeks

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How to submit your revised article: Log into https://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Many thanks again. We look forward to seeing your revised article within 6 to 8 weeks.

Yours sincerely

Jose Merino
jmerino@bmj.com

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), zzz (editorial adviser), [and list other eds who took part]

Decision: Put points (revision required)

Detailed comments from the meeting:

We found the manuscript interesting. Please address all the issues raised by the reviewers as well as the additional points listed below:

1. You mention missing data and using imputation to account for it. But we did not find information in the manuscript about the type of data that were missing and how much. Please include this information in the manuscript.

2. To account for case-mix, you derive models used for prediction. We would like to see more information on how well these models fit the data.

3. The presentation of data in Figures 1-3 may be improved. Instead of having the median / IQR by year in separate plots for either country, would it be possible to combine the plots and have the median/IQR for each country underneath each other for each year, perhaps using different colors to indicate the country? This would make it easier to compare the countries.

4. The population of England and Wales is about 56 million people, about six times the population of Sweden (~9 million people.) The databases used include all patients with AMI in each country. We are puzzled, however, because according to the manuscript, the number of patients admitted to the hospital with an MI was only about 3 times higher in England and Wales (391,077 patients) than in Sweden (119,786 patients.) This suggests that a substantial part of English patients are left out of the analysis, or that the threshold for admittance in Sweden is much lower (Healthy user bias?), or that MI is much more common in Sweden. We would like to see an explanation in the manuscript about this discrepancy and how this issue may affect the interpretation of the study results. Based on the proposed explanation, you may have to qualify your conclusions.

5. Please modify the "what this study adds" in the BMJ style (see instructions for authors.)

Please also respond to these additional comments by the committee:

IMPORTANT
When you revise and return your manuscript, please take note of all the following points. 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.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
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Please include the items below in the revised manuscript to comply with BMJ style:

* the title of the article should include the study design eg "a retrospective analysis of hospital episode statistics"

* ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see ttp://resources.bmj.com/bmj/authors/editorial-policies/guidelines)

* Please complete the following statement and add it to your manuscript:
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* 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:
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For a study of a diagnostic test:
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• PPV and NPV (positive and negative predictive values)

For research articles
As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this file with file designation 'Revised Manuscript Marked copy'.

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
Chung and colleagues seek to characterize variation in guideline recommended care for AMI and associated clinical outcomes in Sweden and the UK. They compare findings from nationwide registry data from both countries using hierarchical, case-mix and volume-adjusted data. They find that Sweden has lower 30-day mortality and less variation in outcomes by hospital. In both countries, the hospital proportion of guideline-concordant care was inversely associated with rates of 30-day mortality.

This works extends the authors' earlier publication (Lancet 2014;383(9925);1305-12) that demonstrated differences in 30-day mortality at the patient level between Sweden and the UK. In the current manuscript, the authors seek to quantify variation in care processes and outcomes at the hospital level, as well as their relationship to one another. The paper makes an important contribution to the literature.

This work is certainly relevant to policymakers, as it shows disparities in guideline concordant care and outcomes between the 2 countries over the study period. It also shows that the UK is narrowing these gaps over time. Although variation in care and outcomes by hospital should also be an important issue to patients, this connection is not always clearly made.

Overall study design is clear and straightforward. STROBE checklist completed adequately. As focus is hospital variation and hospital outcomes, the authors appropriately use multilevel models with case-mix adjustment and weighting for volume, as is done by the Centers for Medicare & Medicaid Services when evaluating hospital mortality performance in the US.

I do have the following questions:

1. Only the first admission was chosen for patients with multiple admissions. Why was a random admission not chosen? Choosing the first admission will systematically under-estimate true rates of mortality (by definition, the first of multiple admissions could not have resulted in death).

2. What was the performance of the models used to calculate receipt of guideline-recommended therapy and 30-day mortality using your 17 case-mix variables?

3. How did your calculation of each hospital's standardized mortality ratio (HSMR) take into account greater uncertainty of estimates from low volume institutions?

4. It did not appear that bootstrapping was done to calculate each hospital's HSMR. If so, why not? This is a standard part of the methodology used by the Centers for Medicare and Medicaid Services in the US to calculate hospital 30-day mortality after AMI.

5. You indicate that multiple imputation was used with missing data for case mix variables. How much missing data was present?

Regarding results:

1. Often hospital-level papers will have a Table 1 that describes the characteristics of hospitals in the sample. As this paper seeks to compare hospital practices and outcomes in 2 countries, it would be helpful to understand a bit more about the hospital sample in both Sweden and the UK.

2. In general, one can paint a very different picture if 2004-2010 results are combined and compared between countries or if just 2010 results are compared between Sweden and the UK. 2010 data seems to show much greater similarity between the 2 countries in terms of both variation in care patterns and outcomes. Why was the former approach taken?

3. In supplemental Table 1, it is not clear that the numbers in each cell refer to medians and IQRs.

Regarding discussion:

1. On page 10, line 22: Am not sure what is the justification for the sentence beginning with "Although risk differences between hospital quartiles…."'

2. Re: limitations on page 11, line 22, you cannot use case-mix standardization as a method to account for unmeasured confounding. By definition, standardization based on case mix tries to adjust for known confounders.

Regarding messaging in general:

You cannot state as you do in the abstract conclusion and discussion that your finding a correlation between guideline adherence and outcomes at the hospital level means that further increasing guideline adherence will further improve outcomes. You would need an interventional study to make this conclusion. Rather, you can state that your results suggest that further adherence to guidelines and reduction in practice variability may improve outcomes for patients.

Additional Questions:
Please enter your name: Kumar Dharmarajan

Job Title: Assistant Professor

Institution: Yale School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

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 (please see BMJ policy) please declare them here: 1. I work under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures.

2. I am funded by a K23 career development award from the National Institute on Aging and American Federation for Aging Research.

Reviewer: 2

Recommendation:

Comments:
Thank you for the opportunity to provide a patient review of this well-written paper. Your study is particularly interesting because, as much as possible, it looks at comparable health care systems, providers, and patient demographics in both Sweden and in the U.K.

The subject of inter-hospital variation in patient care/outcomes is an important one for all heart patients. Indeed, it's an extremely serious issue for both patients and our families because we rarely if ever have any choice in selecting the hospital we trust for our care. And most patients are not even remotely aware of which hospitals are providing AMI guideline-recommended treatments and which are not. We simply show up during an often-terrifying cardiac event wherever the ambulance delivers us, or at the door of the closest hospital, trusting blindly that we will get whatever care we need to get. Sadly, this trust sometimes appears unwarranted.

I find this gap in consistent cardiac care inexcusable, as should all cardiologists – although it's certainly not unique to cardiology. The relevant question I asked in a 2012 blog article I wrote on this subject was: "Why do doctors call it 'practice variation' instead of poor care?"

As a heart attack survivor who was misdiagnosed with GERD during my MI and sent home from the Emergency Department, I'm concerned about all areas of cardiac care (as your paper describes under Policy Implications) "from time of admission through to discharge and beyond" – and not simply whether a patient ends up in the cath lab. (And given the current controversy, particularly in the U.S., around overuse/unnecessary stents, this may or may not be a bad thing).

While reading your paper, I was curious about a possible limitation you mention, namely the fact that you could not evaluate differences in AMI care prior to hospital admission. While you did accept comparable time from symptom onset to hospital admission to explain assumed similarities between the U.K. and Sweden, prior studies have suggested significant variations in routine care provided by ambulance paramedics en route to hospital, particularly to their female heart patients – a

discrepancy subsequently linked to poorer outcomes for those patients (Meisel Z et al. Influence of Sex on the Out-of-Hospital Management of Chest Pain. Academic Emergency Medicine Volume 17, Issue 1, 4 JAN 2010). So just measuring response/arrival time may not be adequate to explain differences in care being provided to heart patients riding in the "back of the bus."

Conversely, your paper did not mention if 30-day mortality rates might also be influenced by incomplete discharge instructions – again, significantly low or even non-existent for many heart patients heading home from hospital. The U.S. report, "Snapshot of People's Engagement in Their Health Care" for example, was published by The Center For Advancing Health in 2010. Although an American paper, it certainly rang true here for Canada where I live). It estimated that 91 percent of patients diagnosed with a chronic illness like heart disease did not receive a written plan of care before being discharged from hospital - again, a gap associated with lower compliance/higher hospital re-admission rates.

I have questions about, of course, your comment that the national registries do not capture all patients admitted with AMI. In addition, because you were unable to determine a number of "unmeasured factors", the question becomes: how can we reliably evaluate something we can't measure without resorting to educated guesswork?

I'd also prefer to see your conclusion, which seemed remarkable in its restraint, express boldness. Instead of recommending "more consistent health care" (a rather soft lob, really, given that no physician or hospital administrator anywhere can possibly claim ignorance of the need to treat patients appropriately and according to accepted practice guidelines).

Indeed, the seriousness of your paper's results (especially hard on the heels of your 2014 Hemmingway/Jernberg paper in The Lancet) warrants an immediate call to action for senior decision-makers, particularly in the U.K. and in the areas surrounding those higher 30-day mortality rates compared to Sweden. Your team has already had the experience of publishing an earlier paper comparing Sweden and the U.K. on a related issue; I'm also hoping you were able to use resulting media coverage to test the waters in terms of assessing government appetite for concrete action.

Once again, thank you for the chance to provide some feedback for this interesting paper, on behalf of the heart patients you will help.

Additional Questions:
Please enter your name: Carolyn Thomas

Job Title: Patient Reviewer

Institution: HEART SISTERS - www.myheartsisters.org

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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 (please see BMJ policy) please declare them here: I have no competing interests / conflicts whatsoever.

Reviewer: 3

Recommendation:

Comments:
Authors Comments:

This is an interesting and well-written manuscript comparing hospital variation in AMI care and outcomes between Sweden and the UK during 2004-2010. Given that all acute care hospitals participate in the respective AMI registries for each country, there is presumably near to complete case ascertainment of AMI in both countries – this is a major strength. However, major weaknesses include the potential large number of unmeasured confounding factors and between country variation in the proportion of STEMI vs. NSTEMI patients that did not appear to be adequately accounted for in the case-mix adjusted analyses.

Comments
1. The selection of the 17 baseline characteristic variables for the case-mix adjustment is not justified with any references and thus appears to not be based upon prior experiences or established risk models like the GRACE model. For example, cardiac arrest before presentation is included (which is good as this is a big driver of mortality in the GRACE model), but Killip Class (including cardiogenic shock) is not included. Also, baseline serum Cr (or estimated CrCl) is not included even though this variable is a very strong predictor of mortality after AMI presentation. Finally, ST segment deviation (STEMI or NSTEMI with ST depression is not included) even though this ECG variable is a strong predictor of mortality. While some of these variables may not have been collected in the respective registries, there should at least be some acknowledgement that key variables for risk adjustment were not collected.
2. More details on the treatments received during the index AMI hospitalization (medications, angiography, and revascularization) should be included and accounted for in a sensitivity analysis for 30-day mortality. These data should be available as reported in a recent manuscript that included data from both of these registries (R.L. McNamara, S.C. Chung, T. Jernberg, D. Holmes, M. Roe, A. Timmis, S. James, J. Deanfield, G.C. Fonarowh, E.D. Peterson, A. Jeppsson, H. Hemingway. International Comparisons of the Management of Patients with Non-ST Segment Elevation Acute Myocardial Infarction in the United Kingdom, Sweden, and the United States: The MINAP/NICOR, SWEDEHEART/RIKS-HIA, and ACTION Registry-GWTG/NCDR Registries. International Journal of Cardiology. Int J Cardiol. 2014 Aug 1;175(2):240-7.)
3. The difference in proportions of STEMI relative to NSTEMI over time is not widely mentioned and is only tangentially shown in Supplementary Table S1. Given differences in proportions of STEMI relative to NSTEMI over time between UK and Sweden, how has this influenced mortality outcomes between UK and Sweden? Does case-mix adjustment including troponin levels sufficiently adjust for this? MI classification (STEMI vs. NSTEMI) should be added to the case-mix adjustment.
4. It is problematic to include revascularization for NSTEMI as a guidelines recommended therapy for analysis in this manuscript for many reasons. First, there is no information provided about revascularization capabilities of the participating hospitals for both countries so there likely was differential access to revascularization that was not accounted for in the analysis. Second, European guidelines for NSTEMI recommend early angiography for high-risk patients with the provisional use of revascularization based upon interpretation of the angiographic findings, patient co-morbidities, and patient preferences. Likely these details were not collected in order to classify a truly "eligible" sub-group of the NSTEMI patients who were actually candidates for revascularization. Finally, it is well know that the lowest risk NSTEMI patients are preferentially referred for revascularization so the differential availability of revascularization in the UK vs. Sweden during the time course of the study introduced a significant amount of confounding.
5. The manuscript has far too much data displayed in the tables and figures. Additionally, the text in the results section recites too much data from the tables and figures and should rather be more concise, focused, and qualitatively refer to the results in the tables and figures. Different methods of data display should be considered and the manuscript should be re-oriented to more a clinical perspective to reduce the heavy focus on statistical methods and results – this would make the manuscript more interesting to the clinical readership of BMJ.

Editors Comments:
I authored this review together with Dr. Kristian Kragholm-Sorensen who is a trainee under my direct supervision. I am submitting this review on our joint behalf.
This is an important manuscript that could potentially be acceptable for publication in BMJ, if major revisions are done and our comments are carefully addressed. If this happens, I believe that an accompany editorial would be very helpful and I would be happy to author such an editorial, working together with Dr. Kragholm-Sorensen, if desired.

Additional Questions:
Please enter your name: Matthew Roe

Job Title: Associate Professor of Medicine, with Tenure

Institution: Duke Clinical Research Institute

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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 (please see BMJ policy) please declare them here: All of my conflicts of interest are publicly disclosed on www.dcri.org. I have no conflicts of interest that influenced this review or that should be considered to be relevant to the topic of the manuscript under review.

END

Date Sent: 26-Feb-2015