Dear Dr. Merino,

Thank you very much. Following the invitation for revision received on 26 February, 2015, I am pleased to revise the manuscript which carefully addresses the comments from the journal's manuscript committee meeting together with three reviewers.

Comments from the BMJ's manuscript committee 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.

The type of data that were missing was information on baseline patient case mix variables. For instance, MI classification (STEMI/NSTEMI) was missing in 2% of Swedish patients. Systolic blood pressure at admission was missing in 12% Swedish patients and 14% UK patients. The case mix variable with highest missing values in Sweden was history of cerebrovascular disease (19%) and troponin measure (29%) in the UK. Overall, the median missing proportion in the 17 case mix variables is 1.5% (interquartile range: 7.5%) in Sweden and 8% (interquartile range: 14%) in the UK.

Change in the manuscript We have now reported in the supplementary appendix the extent of missing values in Sweden and the UK (supplementary appendix session two).

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.

These models fit the data well in both countries. We examined the model fit by the distribution of Pearson residuals and mean square weighted deviation (Pearson chi-square statistic divided by degree of freedom). Pearson residual plots of the case mix models do not show systematic deviation from normality. A value closer to 1 indicates a good fit. From the 21 imputed datasets, the rang of mean square weighted deviation of case mix models for 30-day mortality is from 1.01 to 1.03 in Sweden and 0.96 to 0.97 in the UK, suggesting a good fit.

Change in the manuscript We have edited the manuscript (method) and supplementary appendix (session three) with information on model fit.

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.

We agree it with the comment and edited the display. In addition, we made the change incorporating the third reviewer's comment to simplify the display to the main message. The following summarize the revision made on the displays.

Change in the manuscript
- Revised displays the hospital variation in the use of AMI in-hospital treatment (figure 1) and discharge medications (figure 2) in Sweden and the UK. We use black lines for Sweden and red lines for the UK to increase the readability of the between-country comparison. To simplify the display, the temporal trend of hospital treatment use variation in Sweden and the UK is now illustrated by year 2004, 2007, 2010, instead of year-by-year.

- Revised figure 3 reports the overall and year-by-year hospital variation in 30-day mortality for AMI, STEMI and NSTEMI patients in Sweden and the UK. Following the comment of the committee, the median and interquartile range in the UK is plotted underneath Sweden, and the distribution in Sweden is plotted in different colour (black) from the UK (red).

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.

This is a helpful comment which allows us to clarify our comparison and make our conclusions more robust. Firstly, yes the reviewer is correct that the rate of AMI is higher in Sweden, compared to the UK, at least when based on discharge data (see table below). Within the UK coronary heart disease rates are highest in Scotland, so it is possible that Sweden has an even higher rate compared with (the relevant comparison) England and Wales. Secondly, again the reviewer is correct that registries in both countries may miss patients. We have previously published on this in the BMJ[1] which was cited in our discussion. We suspect that more cases are missed in the UK than in Sweden because the registry in Sweden has been established for a longer period of time. The key point is that patients not included in the registries usually have more comorbidities with a worse outcome, thus the nature of any bias is conservative: the true difference in hospital outcome and variation may be greater in the UK than Sweden than is reported in the manuscript.

Table: Hospital discharges ischaemic heart disease rate (per 100 000) in Sweden and the UK by year.

	2004	2005	2006	2007	2008	2009
Sweden	794	762	743	740	688	621
UK	504	488	471	458	444	421

Source: WHO Europe. Health for All Database (HFA-DB) http://data.euro.who.int/hfadb/

Change in the manuscript We have edited the manuscript (discussion) adding the observation of greater AMI admission rate in Sweden and the UK to the second paragraph on the hospital treatment variation.

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

The session is now modified accordingly.

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.

We thank the reviewer for this view that our paper extends previous work and makes and important contribution.

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.

We thank the reviewer for this comment about the patient relevance of our paper – which we note is shared by the patient reviewer.

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).

We consider our approach robust, valid and clinically the most easy to interpret. We agree with the reviewer that the aetiology and prognosis of second and subsequent AMI may differ from those of the initial AMI episode and, particularly important to our paper might have different country specific health system influences. This is an argument for seeking to identify a relatively 'pure' first AMI in order to make more clear comparisons. We applied the same method to identify the index AMI admission in both countries to reduce the likelihood to include subsequent AMI.

Change in the manuscript We have edited the manuscript (limitation) to address the reviewer's comment.

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?

The models performed well, judging by the goodness of fit of model to the data in both countries. We examined the model fit by the distribution of Pearson residuals and mean square weighted deviation (Pearson chi-square statistic divided by degree of freedom). Pearson residual plots of the case mix models do not show systematic deviation from normality. A value closer to 1 indicates a good fit. From the 21 imputed datasets, the rang of mean square weighted deviation of case mix models for 30-day mortality is from 1.02 to 1.03 in Sweden and 0.96 to 0.97 in the UK, suggesting a good fit. Similar results were observed in treatment modelling.

Change in the manuscript We have edited the manuscript (method) and supplementary appendix (session three) with information on model fit.

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

We agree that low volume institute will have a greater uncertainty in hospital proportions due to small sample size. In our manuscript, instead of restricting the analysis to hospitals with volume above an arbitrary cut off, we use volume-weighted analysis to allow all hospitals of the country to contribute in the analysis, taking into account the greater uncertainty in estimate from hospitals with small volume.

We did not adjust for hospital volume in calculating the hospital's case mix standardized mortality ratio, since strictly speaking, admission volume was not a case mix characteristic. Reflecting on your comment, we perform sensitivity analysis restricted to hospitals with admission volume more than 30 (5 among 87 hospitals in Sweden, and 3 among 242 hospitals in the UK), and the distribution of hospital standardized mortality ratio is 8.5% in Sweden and 9.7% in the UK, with the interquartile range of 2.4% and 3.5%, respectively. Comparing to the case mix-standardized hospital 30-day mortality reported in the manuscript (median and interquartile range 8.4%, 2.6% in Sweden and 9.7%, 3.5% in the UK), the

influence of small volume hospitals on study result is little. We thus include all hospitals in the analysis, for the estimates to be based on the entire patient and hospital population.

Change in the manuscript We have included the sensitivity analysis excluding hospitals with admission volume less than 30 in the supplementary appendix (figure S2).

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.

Bootstrapping was not used in the present study. Bootstrapping is used in selecting variables to develop risk model from Centers for Medicare and Medicaid Services claims data. As we included all case mix variables which are comparable in both countries in the model, variable selection method and bootstrapping was not required in our study.

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

Please refer to our reply to the first comment from the BMJ's manuscript committee meeting.

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.

We agree this would be helpful but as the reviewer may be aware there is a lack of international standardised data on hospital characteristics. We have added hospital volume, the comparable hospital-level variable between the two countries, to the summary of hospital case mix information in Sweden and the UK (supplementary table S1).

Change in the manuscript We have edited the manuscript (results and discussion) and supplementary appendix (table S1) with information on hospital volume.

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?

The main reason we reported 2004-2010 results and investigated hospital treatment and outcome change over time, instead of studying 2010 alone, is for the secondary study objective of understanding secular change in hospital AMI care practice. We have reported in the results and discussion the overall and by year findings.

Change in the manuscript We have now revised the manuscript (introduction) to clarify the relevance of including the time trends in both countries.

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

To clarify the statistics displayed in the table, we have now changed the title of supplementary table 1 to 'Median and interquartile range of hospital-specific case mix proportions and mean values by admission year in Sweden and the UK', instead of the original title 'Distribution of hospital-specific case mix variables in Sweden and the UK'.

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…."'

We now provide the justification in the supplementary session four. Table S4 summarized the case mix standardised mortality by hospital treatment quartiles, and estimated deaths delayed or prevented if hospitals of the lower treatment use quartiles (Q1-Q3) had hospital case mix-standardized mortality in the highest treatment quartile (Q4). The greatest mean difference in risk-standardised mortality observed between the lowest and highest hospital use quartiles was primary PCI for STEMI in Sweden (2.4%), any reperfusion and discharge dual antiplatelet in the UK (0.9%). Compared to hospital reperfusion therapy use quartiles, difference in case mix standardised mortality between the highest and lowest hospital use quartiles was smaller for most discharge medications.

In absolute number of death prevented or deferred, decreasing the case mix standardised mortality discrepancy between hospital primary PCI use quartiles resulted an estimated 581 lives saved in Sweden, and 1013 lives saved in the UK. Deaths prevented or deferred from decreasing mortality difference between hospital discharge mediation use quartiles was estimated to be 573 in Sweden and 2274 in the UK for dual antiplatelet, 574 for statin in Sweden, and 1579 for beta blocker In the UK. The similar or greater estimated number of lives saved by hospital practise variation in discharge medications use than reperfusion was due to the greater patients population (all AMI survived the acute infarct) may be benefited from the use of discharge meditation than reperfusion therapy for STEMI patients alone.

Change in the manuscript We have now revised the manuscript (discussion) and supplementary appendix (session four) to include more information on estimation and interpretation of deaths prevented or deferred.

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.

We agree and have revised the manuscript (limitation) accordingly.

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.

We agree and have revised the manuscript (abstract and discussion) accordingly.

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.

Thank you. We are really pleased to see such a helpful patient review. As the reviewer says UK and Sweden are sufficiently similar (health service free at the point of use, % GDP spent on health) that it makes comparison worthwhile.

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.

Again helpful. What patients care about is how good is the care and outcomes I am likely to receive in my hospital? Could it have been better elsewhere? There is as far as we are aware no other paper that examines these variations between 2 countries.

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?"

Helpful. We have revised the manuscript using where appropriate the terms of 'unacceptable practice variation' and 'poor quality 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).

Thank you. The whole spectrum of AMI care, from primary care to hospital care and post acute phase management is our area of research focus.[2-4] We could expand on this if the editor wishes.

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."

We agree that Emergency Medical Service (EMS) has an important role in integrated AMI care pathway.[5] Proper analyses on EMS may be beyond the scope of our study, but will be a definite future step, which has been described in the future research session of the manuscript.

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.

Thank you, the comment is important and we agree that coronary heart disease might helpfully be considered as a long-term chronic condition, punctuated by acute episodes. Involving patients in the development and communication of evidence based discharge plan is important and may improve the care and outcome. We have added this to the discussion.

I have questions about, of course, your comment that the national registries do not capture all patients admitted with AMI.

Yes, and please refer to our reply to the four comment of BMJ's manuscript committee meeting.

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?

This is helpful in tightening our manuscript. Firstly we what we have measured does allow us to make reliable evaluations. Our study was based on the only ongoing nationwide clinical registries; and measures are based on clinical guidelines and professional led views of what is important for case mix, treatment and outcome.

Secondly we agree that it is important to be more explicit about the 'unmeasured' and what types of data would be informative. Broadly there are two strategies: first and most important we think there is a major role of accessing measures that already exist in these patients but have been hard for researchers to access. In this sense 'unmeasured' should be replaced by 'measured but unavailable'. Each of these patients will have 1000s of measurements made on them and recorded in diverse electronic health record systems before during and after hospitalisation. This would include LV function, a measure of socioeconomic status and so on. Second, there is a role for measures that do not exist and need creating.

We have edited the manuscript (discussion) to include the importance of accessing the currently 'measured but unavailable' data in future research.

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).

We agree. We have edited our conclusion as follows: 'High quality health care across all hospitals, especially the UK, toward better use of guideline recommended treatment, may not only reduce unacceptable practice variation, but also deliver improved clinical outcomes for patients with AMI.'

Indeed, the seriousness of your paper's results (especially hard on the heels of your 2014 Hemingway/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.

Thank you, we agree. We think our results have wide international interest. (Patients in any country should ask what is their own between hospital variability in care and outcome, and if it is not known why not?). In the UK in the run up to the general election on May 7th 2015 we think our results are highly topical. In the Farr Institute and NICOR we have appropriate stakeholder involvement to channel our findings for policy relevance.

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

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.

Thank you. As far as we are aware UK and SE are the only two countries that can attempt such an analysis which reviewers consider of high patient relevance. The US, Denmark and other countries do not have quality and outcome registries for AMI with participation from all hospitals.

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.

We do not agree with this comment (what is this 'large number') nor do we think that this is likely to alter the conclusions. Nonetheless it is helpful to allow us to clarify our approach.

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.

We are pleased to clarify how both points are incorrect. First our models are indeed based on prior experience in these data[6]. Second the models were of course based on reference of validated prognostic models.[7,8]

We justify variable selection on clinical a priori grounds. We sought to account for MI type (STEMI/NSTEMI), MI severity (troponin level, admission HR, admission BP), demographic factors, risk factors, comorbidity, and pre-hospital treatment. We regard this as comprehensive case mix adjustment - there are no other 'case mix' variables present in both these quality registries throughout the study period. The variables we adjusted for are those which the professional judgements of the two whole health systems deem worthy of recording (for the purpose of case mix adjustment between hospitals).

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.

The case mix model in the study accounts for the NICE mini-GRACE risk score,[8] as variables used in the mini-GRACE score (age, heart rate, systolic BP, ST-deviation on ECG, cardiac arrest at admission, elevated cardiac enzymes) are included in our case mix adjustment. The concern we have for the reviewer comments is that applying mini-GRACE score only might leave residual case mix unaccounted than the 17 variables case mix adjustment. It is showed by the greater AIC values (smaller AIC value means better performance in generalised mixed model) from the model included mini-GRACE variables only than the case mix model in the study, indicating less optimal performance. In addition, the mortality outcome mini-GRACE score focused on is 6-month mortality, different from the primary endpoint of the study (30-day mortality), reducing the applicability of the mini-GRACE risk score in the present study. Therefore, we decide to keep using the case mix model in the study.

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.

The issues of additional prognostic factors only arises insofar as they add prediction beyond the variables already included in the model. The reviewer provides no evidence that e.g. Killip class adds information beyond admission age, HR and SBP and heart failure; likewise no evidence that serum creatinine, ST segment deviation adds information beyond the 17 variables in our model. For example, our sensitivity analysis results showed that the AIC values for case mix adjustment including serum creatinine is exactly the same with the original 17 variables case mix adjustment, indicating serum creatinin did not add to the model in addition to existing case mix variables.

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 Journal of Cardiology. Int J Cardiol. 2014 Aug 1;175(2):240-7.)

We thank the reviewer for citing our previous publication, which was referred in the manuscript discussion. We decide to report hospital-level rate throughout the manuscript. As the specific aim of the study is hospital variation, it provides clarity and helps the reader to focus on hospital level for the manuscript to report hospital-level rate throughout.

Based on your comment, we have now performed a sensitivity analysis for 30-day mortality, accounted for patient case mix, volume and treatment. The median case mix and treatment standardized mortality is 7.3% in Sweden and 9.9% in the UK, with the interquartile range of 2.3% versus 3.1%, respectively. The results provide additional support to the main finding in the study of a greater hospital variation in the UK than Sweden, and are included in the supplementary materials.

Change in the manuscript We have edited the manuscript (discussion) and supplementary appendix (figure S3) with information on hospital case mix and treatment standardized mortality.

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.

Yes, proportion of STEMI admitted to the hospital is one of the hospital-level case mix characteristics reported.

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?

We consider the differences in hospital admission STEMI % over time between Sweden and the UK may not influence much in the hospital mortality between the two countries. This is based on our finding (figure 4 of the manuscript) where we illustrate a trend of decreasing hospital volume-weighted AMI 30-day mortality over years in both countries, and the same trend was observed in both STEMI and NSTEMI patient subgroups in Sweden and the UK.

We included STEMI/NSTEMI information in the case mix adjustment to sufficiently control for the confounding due to STEMI/NSTEMI. Including troponin levels in case mix was more for adjusting for the severity of the infarction than STEMI/NSTEMI in the analysis.

MI classification (STEMI vs. NSTEMI) should be added to the case mix adjustment.

We agree (it already was).

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.

Although the guideline recommendations for revascularization at NSTEMI are more complex than for STEMI, we think it is important to highlight also the over time and between country differences in this important treatment modality. The relevance of this indicator of quality of care is emphasized by the findings in the study where there from 2004 - 2010 in UK was an increase from 2% to 35% and in Sweden from 26% to 44%. Considering that early revascularization have been shown to improve outcomes in intermediate or high risk patients with NSTEMI, these differences over time and between the countries have probably contributed to the observed continuous reduction and decreasing difference in mortality at NSTEMI between the two countries. Therefore the inclusion of this core component of the

treatment of NSTEMI can not be excluded when studying quality of care and its relation to outcome in NSTEMI.

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.

Correct we do not have angiographic findings, and we now specify this in limitation.

Change in the manuscript We have edited the manuscript (limitation)

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.

Although the current study is unable to sort out the eventual reasons for performance of revascularization such as "the interpretation of the angiographic findings, patient co-morbidities, and patient preferences indicating the true candidates for revascularization" still the dramatic changes over time in both countries indicate that in-hospital revascularization in NSTEMI actually worked out as an important indicator of quality of care in the cohorts from both countries. Acknowledging the larger complexity in the revascularization recommendations at NSTEMI we have adjusted the text on the treatment recommendation to read: " revascularization (PCI or CABG) as appropriate and feasible and anticoagulant (unfractionated heparin, low-molecular-weight heparin or Fondaparinux) for NSTEMI patients".

Change in the manuscript We have edited the manuscript (discussion).

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.

As suggested, we have simplified the displays to the main message. Please refer to our reply to the third comment from the BMJ's manuscript committee meeting.

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.

The following is the reference cited in the response letter.

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2. Denaxas SC, George J, Herrett E, et al. Data resource profile: cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). *International journal of epidemiology* 2012; **41**(6): 1625-38.
3. Boggon R, van Staa TP, Timmis A, et al. Clopidogrel discontinuation after acute coronary syndromes: frequency, predictors and associations with death and myocardial infarction--a hospital registry-primary care linked cohort (MINAP-GPRD). *Eur Heart J* 2011; **32**(19): 2376-86.

4. Rapsomaniki E, et a. International comparison of outcomes among 140,880 patients stable after acute MI; real world evidence from electronic health and administrative records. ESC Congress; 2014; 2014.
5. Herrett E, Bhaskaran K, Timmis A, Denaxas S, Hemingway H, Smeeth L. Association between clinical presentations before myocardial infarction and coronary mortality: a prospective population-based study using linked electronic records. *Eur Heart J* 2014; **35**(35): 2363-71.
6. Chung S-C, Gedeborg R, Nicholas O, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014; **383**(9925): 1305-12.
7. Morrow DA, Antman EM, Giugliano RP, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet* 2001; **358**(9293): 1571-5.
8. Simms AD, Batin PD, Weston CF, et al. An evaluation of composite indicators of hospital acute myocardial infarction care: a study of 136,392 patients from the Myocardial Ischaemia National Audit Project. *International journal of cardiology* 2013; **170**(1): 81-7.

Thank you.
Yours sincerely,
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