PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Developments in the invasive diagnostic-therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2011: A nationwide cohort study
AUTHORS	Hansen, Kim; Sørensen, Rikke; Madsen, Mette; Madsen, Jan; Jensen, Jan; von Kappelgaard, Lene; Mortensen, Poul; Galatius, Søren

VERSION 1 - REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna Italy
REVIEW RETURNED	06-Feb-2015

GENERAL COMMENTS	The authors have shown that women are 15% less likely than men to undergo coronary angiography within 60 days from admission for an ACS. Similar but less pronounced differences were found for subsequent revascularization, The cumulative incidence for revascularization within 60 days had an adjusted HR of 0.93 (0.90-0.96). There are some points that deserve more information and/ or discussion. (1) The paper confirms that in women, normal/non-significant CAD is highly prevalent. Women with chest pain, whether it is acute coronary syndromes or otherwise are not as often represented in the catheterization laboratory as men. However, the different twist to this manuscript is that when they are represented in the catheterization laboratory, they have the same aggressive interventional as the men who undergo cardiac catheterization. To me, that's the main message of this manuscript, and I would suggest repackaging some of the discussion and citations on this issue. (2) The other point is that perhaps aggressive invasive management of the patients not referred to the catheterization laboratory would decrease cardiovascular endpoints. However, that's speculation, since there are no data contained in this manuscript that address that issue. Does this apply to those patients having STEMI or non-STACS? In the manuscript we have data on the entire cohort of patients. I suggest separating the cohort of patients with STEMI from those with non-STACS, as guideline driven recommendations for coronary angiography, and PCI are quite different for STEMI and non-STACS. (3) Methods and results: more details are needed for Model 4 (adjustment for extent of coronary disease), which is a critical issue

	in the study. (4) Discussion and conclusions: the authors state that “the question, of whether a differing invasive approach in women and men represents a clinically appropriate strategy, an overuse of cardiac catheterization in men or an actual underuse in women, needs to be addressed adequately”. You, therefore, indicate that findings suggest that an increase in catheterization rates in women would have certainly increased the number of patients with obstructive coronary disease being identified, but whether this may have produced improved outcomes is uncertain. I agree. For this reasons, I suggest you report separately the data for STEMI and non-STACS, and also the time to cath in STEMI. Rapid medical intervention is essential to the successful treatment of patients with STEMI because PCI greatly reduces the risk of arrhythmias and death.

REVIEWER	Clive Weston College of Medicine, Swansea University, Wales, UK
REVIEW RETURNED	09-Feb-2015

GENERAL COMMENTS	In this research paper the authors use data linkage, between established validated national disease registries and administrative datasets, to explore gender differences in the management of patients presenting with acute coronary syndrome throughout Denmark over a 7 year period. They demonstrate differences in pre-event characteristics between men and women; differences in the proportion of men and women admitted to differing types of hospital in the early management of their coronary events; differences in the use of diagnostic coronary angiography; differences in the angiographic extent of coronary disease; and differences in subsequent revascularisation. They show that despite these various differences there is no difference in outcome (when outcome is expressed as a 60-day fatality rate). This important point – no difference in outcome despite clear differences in process – should appear in the abstract. Interestingly during the period studied, changes in the uptake of diagnostic angiography and revascularisation were similar in men and women so there was no apparent “narrowing” of the gender difference. Strengths & Weaknesses In common with other registry research, the authors point to limitations related to unmeasured potential confounders that may (partly) explain the gender differences. Categorical variables (e.g. heart failure: yes/no) tend to be recorded in such registries, rather than grades of variable (e.g. severity of chronic kidney disease). Most large registries have significant amounts of missing data in the dataset (which contains multiple items for each individual case). It is unclear how such missing data was addressed in this particular study. The analysis appears reasonable. And the strengths and limitations of the study are well-presented with good contextual introduction and a well written discussion.

	The major strength is the use of “big data”/data linkage for a complete nation over a prolonged period of time. I agree with the authors that it is unfortunate that no distinction can be made between ST elevation myocardial infarction and non-ST elevation MI – but this is a weakness of the chosen ICD coding system. Discussion & Questions It is stated that men tend to live further away from hospitals with cardiac catheter facility than women, yet are more likely to be admitted directly to such hospitals. Some of this, I suppose, may relate to an increased proportion of patients with ST elevation being transferred directly to a PCI centre. However, the relevant distance is calculated using the patient’s home address and this may not be the same as their location at the time of onset of symptoms. It’s possible that more men (given the age ranges) are at a place of work during the onset of symptoms and therefore could be closer to a catheter facility at the onset of the event than older women on their own at home. There is no calculation, or description, of the time of onset of symptoms and delays to hospitalisation following onset of symptoms. I assume that there is no obvious gender difference, with increased delay from onset of symptoms to admission to hospital in female patients. Occasionally (in the UK at least) patients experience symptoms of their index event many hours (or even >24 hr) before alerting the medical services, and urgent angiography is probably less important in these cases of delay. It is also very interesting, if I understand the findings correctly, that only 34 patients (from almost 60,000) died on the day of admission. This seems a very small proportion. I’m assuming this is more to do with coding issues and qualification for entering the acute coronary syndrome registry than it is the natural history of coronary disease. Is there any evidence that pre-hospital triage, including ECG analysis of the ST segment, is performed more frequently in men than in women in Denmark? It has been suggested elsewhere that ambulance paramedics are less likely to perform ECG recordings in female patients than in males, and this could lead to more accurate diagnosis and preferential transfer to ‘invasive’ hospitals for men compared with women. With respect to diagnosis, the paper could reference the recent BMJ publication from the group in Edinburgh suggesting that Troponin estimation should have a different (lower) cut point for women than for men [though what effect this would have on the main message (that men and women are managed differently) is unclear]. It would be useful to have some more discussion as to the frequency of unobstructed coronary arteries in this group of patients with acute coronary syndrome. What does this say about diagnosis, pathophysiology and management that so many more women than men going forward for angiography have unobstructed coronary arteries?

REVIEWER	Sofia Sederholm Lawesson Department of Medical and Health Sciences, Division of

	Cardiovascular Medicine, Linköping University, Sweden
REVIEW RETURNED	16-Feb-2015

GENERAL COMMENTS	As regards ethics: Participant consent is not commented and I presume it was not asked for in this retrospective registry study as the authors claim no ethical approval was needed in spite of merging several data bases. Declaration of Helsinki is not mentioned. As regards study design: The study population, registries and statistics are described properly in the manuscript and the discussion is informative and well balanced - but as the author themselves touch upon - the question whether there exist an inappropriate sex difference in the use of coronary angiography and subsequent revascularization cannot be answered by using this type of registries. Anyhow the findings are still interesting and merits publication after revision as it indicates the need of more studies addressing this question. Specific comments to the authors - see below: Review BMJ Open Feb. 2015-02-14 Developments in the invasive diagnostic-therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2001: A nationwide cohort study Background Since decades it is known that men and women differ in several aspects when falling ill into ACS. Women are older with higher co-morbidity, have more often UAP and non-obstructive disease but less often STEMI. In NSTE ACS, more solid evidence of an early invasive approach has been found in men, but among high-risk patients, also women benefit from such a strategy. A sex difference in the use of invasive procedures has been shown in plenty of ACS studies, but if temporal trends have changed according to new knowledge would be of interest to explore. The aim with the present study was to investigate trends in sex differences in the use of invasive coronary procedures in Danish ACS patients 2005 to 2011. The cohort included patients aged 30-90 years with a first-time diagnosis of MI or UAP in the Danish National Patient Registry. Data on co-morbidities was taken from the same registry. Data on invasive procedures was taken from the Danish Heart Registry containing data on all coronary angiography and PCI procedures since 2000. Also other registries were used collecting information about vital and socioeconomic status. The main finding was a 15% less chance of DCA within 60 days in women adjusting for age, co-morbidities, admission year, prior revascularization, distance to PCI-hospital and socioeconomic status. Adjustment for type of ACS (MI or UAP) was not done, but the authors claim that a sensitive analysis on only MI patients showed similar results. No interaction between sex and year of admission was found. Among patients with 2- or 3-vessel disease no difference in subsequent revascularization was found, whereas among patients with 1-vessels disease women had 8 % lower chance of revascularization after multivariable adjustment.

Major issues

- A major limitation is the inability of discrimination between STEMI and NSTEMI/NSTE ACS in combination with lack of important clinical and angiographic data. The mixture of UAP, NSTEMI and STEMI is problematic because of the well-known sex difference in type of ACS mentioned, but also as the benefit of an early invasive strategy in NSTE ACS differ between the sexes, and thus adjusting for a risk score in this subset of ACS patients would have made the results more solid. In this study, as MI is a more robust diagnosis than UAP (the authors state that the positive predictive value for MI was clearly higher than for ACS in the used registry), I think only MI should have been the inclusion criteria, or at least the results should be stratified for type of ACS.
- No patient with a diagnosis of ACS should be discharge on the admission day. According to the authors this was done in 7% (4399/59031 patients). In the same way 1-day mortality of 0,0006% (34/59031) is very low. This raises questions about the quality on the registry and merits an explanation.
- Age is a vital confounder in these types of studies and it is important how this variable is handled in the multivariable analyses. In the present study age was categorised into 10-year intervals and included in the multivariable analyses as a category variable. I would like an explanation why age was not handled as a continuous variable in 1-year steps, possible after some form of transformation if needed. What was the result if age was handled as suggested?
- Outcome measure regarding DCA: Coronary angiography for STEMI should be performed immediately and in NSTEMI within a few days, i.e. the 60 day time limit is questionable. Comparing DCA within 1 day between genders is problematic when no data on MI subtype is available as men have STEMI more often than women. I would suggest DCA during index hospitalization is the main outcome measure, or if not possible, within 1 week.
- Outcome measure regarding revascularization: In 15% of the patients undergoing coronary angiography, the extent of coronary disease was not known. Probably a higher extent of women than men had non-obstructive disease also in this sub-cohort. Examining possible sex-differences in revascularization in patients undergoing DCA is only meaningful in the sub-cohort where significant coronary lesions were found and analyses should therefor be restricted to that sub-cohort, adjusting for extent of CAD. In my opinion Table 4 can be omitted and replaced by explored data from Figure 3, with added information of ingoing variables in the multivariable models.
- As the scope of the whole study is development over time in the sex-differences of use of invasive coronary procedures I would have preferred showing the time trends in more illustrative way, such as showing time trends or stratifying the cohort on inclusion year (or 2-years together) instead of just using an interaction term.

Minor issues

- Important confounders are missing such as data on renal function and possible anemia. The risk of bleeding and complications due to the invasive procedure are higher in women.
- Data on ad-hoc PCI is missing.
- Kaplan-Meyer curves could be omitted as unadjusted data says very little about pure gender differences.
- Inconsequent presenting of $p<0.001$ in the tables, see table 1 and 3. For some variables the p-value is probably missing.

	Summary If a lower chance for women to undergo DCA among high-risk NSTE ACS patients within index hospitalisation could be shown with no change over time, this would be an important finding. In STEMI we have used the Swedish quality registry for MI care, SWEDEHEART, in order to explore temporal trends of reperfusion and other evidenced-based therapy, finding a gender gap that did not diminish during the studied time period (Sederholm Lawesson, BMJ Open, 2012). In the present study a registry including only information on diagnoses of hospitalizes patients was used and thus important clinical and angiographic data is missing. Thus, the finding of a gender gap in the use of DCA among unselected hospitalized ACS patients is interesting but the question whether this gap is inadequate or not merits further studies. The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.

REVIEWER	Gabriel Fabreau Clinical Assistant Professor General Internal Medicine Faculty of Medicine and Community Health Sciences University of Calgary | Cumming School of Medicine
REVIEW RETURNED	20-Feb-2015

GENERAL COMMENTS	This study addresses a health policy question of significant salience. Despite the importance of the scientific question, the strength of the database, the overall quality of the writing the authors should address several important limitations. The following comments and requests for clarification are offered with the goal of strengthening the manuscript. Summary: This is a contemporary Danish registry population-based study on trends in the invasive therapies and diagnostics among patients with ACS. 2005-2011. The main outcome of interest is sex disparities in the receipt of diagnostic cardiac catheterization and revascularization procedures (PCI and CABG) in setting of acute coronary syndromes (STEMI, NSTEMI, UA). The impetus for this study was motivated by recent public health and health care system interventions in Denmark aimed at improving access to streamlined and evidence-based care and a public awareness campaign specifically dedicated at reducing previously identified sex-disparities in care of cardiac patients. Data sources included the Danish National Patient Registry, Danish Heart Registry, Danish National Prescription Registry, Danish Register of Causes of Death and Statistics Denmark. Overall the data source is excellent, the methods appear to be quite sound and the writing very good. The discussion is thoughtful with a good understanding of the state of the current literature with respect to sex disparities in ACS. The authors are quite insightful about the limitations of the study and measured in their conclusions which is a strength. My major criticism of this study is that overall in its current form adds little to the current state of knowledge. I feel that given the strength of their data source and methodology, more could have been done in this regard. In my opinion, the issue of disparity in the receipt of DCA or revascularization alone without investigation of clinical outcomes significantly limits the salience of the analysis. Mortality data is available in their data source, yet it was only

	investigated briefly in an age-adjusted analysis and not in the context of use of these invasive cardiac procedures. Additionally, it is implied that the investigation of these invasive cardiac procedures represents a measure of the quality of care received between the sexes, and alone this may be incomplete. For example, data are presented on medication use on admission for men and women and the receipt of evidence-based therapies in the context of ACS may be another useful measure of quality of care. It would be an interesting addition to the analysis to investigate the use of evidence-based medical therapies between the sexes for ACS on discharge if available. Previous work has shown sex disparities in this context (1-3) and, if found in this cohort, would strengthen the argument for the presence of inappropriate gender bias in the care received between the sexes. The authors correctly point out that appropriateness of use of these invasive procedures is a critical factor that requires further investigation. Unfortunately, as the authors point out there are limitations in the data that prevent this analysis. To this end, I believe the most interesting aspect of this study was the investigation of effect modification by extent of coronary artery disease on receipt of revascularization (Figure 3). It is known that women have less obstructive CAD, and in this study the bulk of the disparities in revascularization appear to be entirely appropriate as they are largely among subjects with no significant stenosis thus, likely not representative of unwanted gender bias. Other factors worth considering in their interpretation/discussion: Gender bias among physicians (4,5), differences in presentation with ACS (6) patient preferences for invasive procedures vs. conservative management, and age-related effect modification by sex (7). Abstract: Concise and well written. If space allows, I would suggest inclusion of the results of the effect modification by extent of coronary artery disease on revascularization analysis as an important finding of this analysis. This analysis would need to be motivated briefly as well. Introduction: The introduction is well written and clearly motivates the impetus behind this analysis explaining recent policy and care changes in Denmark. • It would be helpful to include more information about the Danish Heart Foundation public awareness campaign on sex-related differences and perhaps a reference. If this campaign was specifically designed to reduce known sex disparities readers may appreciate a better understanding of what modalities it used and if any portion of it was focused at healthcare providers who are often those who make treatment and triage decisions for different therapies and transfers to major hospitals when appropriate. • Also, there is an inherent presumption that the impetus to reduce sex-related disparities in treatment is to also improve the outcomes of care, however sex-differences in clinical outcomes after ACS are not mentioned (mentioned above in global summary). Methods: The data sources are very good and truly population-based (Entirety of Denmark). Good explanation of definitions used for primary diagnosis in Denmark (important for context). The authors used validated definitions of AMI within the data sources used. They also used validated invasive cardiac procedures and prescriptions. All strengths. Specific comments:

	• Page 6: Please provide more information about data from Statistics Denmark: “Information on emigration, income, level of education, cohabitation status, and distance to hospitals with cardiac catheterization facilities were collected from Statistics Denmark.” Is this information individually reported or aggregated area-level data from a national census? • Page 7, paragraph 2: Exclusions are reasonable however I don’t believe that those that die on the same day of admission may all be necessarily ineligible for cardiac catheterization. For example, a severe ACS may go for an emergency procedure and have a fatal arrhythmia on the table in the cardiac catheterization laboratory, but not be included in this study. As only 34 patients of the entire cohort were excluded in this way I doubt that their inclusion will affect the study results and may improve validity by avoiding this criticism. • Page 7, paragraph 3: “Only a minor group was self directed or referred to emergency departments from their general practitioner.” Please clarify how many patients this represents (proportion) and if possible, whether there is a gender disparity in this patient population. • Page 8, paragraph 2: The outcomes measures are reasonable except Table 1 (page 24) lists revascularization rates for within 1, 3, and 60 days and the methods only mentions revascularization within 60 days. • Age adjusted 60-day mortality rates are presented in the results section (page 10, paragraph 4) but this analysis is not introduced in the methods section. Additionally why this outcome was only adjusted for age is not justified in the methods section? This is especially confusing in light of the citation of the Ontario MI prediction rule for 30-day and 1-year mortality (page 9, paragraph 1) as justification for inclusion of comorbidities in the analysis for the receipt of coronary angiography. • Page 8, paragraph 3: Please explain why age was categorized into 10 year intervals and included as a categorical variable. I don’t understand the value of this as age is always a very important predictor of both treatment and outcomes. By categorizing this variable there is a loss of information and statistical power. • Socioeconomic status by net annual family income needs to be clarified. Is this census-derived area-level family income or individual household reported? Additionally the categorization into low, medium and high needs to be defined in a monetary figure and justified. • Highest educational level achieved similarly needs to be clarified and defined (ie. years of education or level of education in each category) • What geographical program was used to perform the distance calculations between patients’ homes and nearest hospital? Please include in the methods section. • The number of hospital transfers is included in Table 1 (page 24) but not mentioned in the methods section. Please clarify how this variable was calculated • Page 8, paragraph 4: “Diagnoses of heart failure, cardiogenic shock, dysrhythmia and pulmonary oedema indicated the severity of heart disease”. While this is reasonable, heart failure can be a pre-existing chronic comorbidity. Was the presence of CHF on presentation as a marker of severity of ACS distinguished from CHF

as a comorbidity?
• In the adjusted models presented in Table 2, it is not clear if these above markers of severity of ACS are included in the adjustment. “comorbidity” is listed but these markers of ACS severity are not comorbidities and if included in the models should be clearly stated.

• Page 9, paragraph 1: Why was revascularization within 3-years of the index event only included in the analysis? The justification provided is that this may influence the decision to pursue invasive examination, but presumably the receipt of a CABG 4-years before the index event would be as likely to influence these decisions.

• Statistical Analysis: How was the clustering effect modelled in their cox models? What correlation structures were assumed and what statistical procedures used?
Results:
• It is not clear why age-adjusted 60-day mortality was chosen to be presented instead of fully adjusted mortality outcomes.
• Spelling out the cumulative incidences from Figure 1a does not add any information not already presented in the unadjusted rates of each invasive procedure in the sentence above. Stating the unadjusted HR’s would suffice.
• Page 12, line 42: “female gender was associated with slightly lower rate of PCI”. It would be helpful for the reader to clarify that these are adjusted rates again
• The last section of the results that discusses the interaction between coronary artery disease and receipt of invasive procedures is likely the most interesting part of this analysis and novel. I would elaborate on this section somewhat. Also, this analysis feels like it comes out of nowhere as it was never motivated in the introduction as to why you think this should be the case. This analysis was not explained in the methods section either, thus contributing to my feelings of surprise. I suggest doing both
• Lastly, the unadjusted rates of revascularization by extent of coronary artery disease should likely be presented. The adjusted OR of 0.47 for revascularization among women compared to men is a large effect size. It would be helpful to know what the rates are that are associated with the adjusted and unadjusted results presented in Figure 3.
• Table 2 and Table 3 should be reversed in order. Table 2 presents the adjusted results and should come after Table 3 with unadjusted comparisons and description of coronary artery disease severity
• Figures: Please list the covariates that are included in the adjusted models in a footnote below the Figure 3.
• Table 2 has a footnote that explains model 4 has a smaller sample size (n=48 609). This is not explained in the methods section. Missing data, if significant should be addressed in the methods and how it was handled, as it can add important selection biases.
Discussion:
• In the limitations section in page 14, when discussing the lack of core clinical variables as a potential source of unmeasured confounding. I would also include that the use of these variables would allow for a validated severity score of ACS at presentation and would allow a mechanism to assess appropriateness of DCA between the sexes.
• The authors should concede that the lack of clinical outcomes in this analysis is a major limitation in their ability to interpret the sex disparity in the receipt of invasive cardiac procedures that they have identified.
• In the interpretation of the results implicit gender bias is not

	discussed as a possibility to explain the disparities identified, although this has been identified in previous studies. Additionally, there was no mention of the differences in symptom presentation between men and women with ACS as a potential explanation that may effect physician decision making as well. • The final sentence of the discussion raises the question about clinical appropriateness and the need to investigate overuse/underuse. This implies understanding the clinical outcomes resulting from these disparities and should be clarified. Minor Points: • Typo: Page 11, line 33: “to omen” • Page 11, paragraph 1: “Despite living a bit further from hospitals”. Minor point, colloquial English should be edited • Typo: page 12, line 26: “toomen” References 1. Opotowsky AR, McWilliams JM, Cannon CP. Gender Differences in Aspirin use Among Adults With Coronary Heart Disease in the United States. J GEN INTERN MED. 2007 Jan 9;22(1):55–61. 2. Moriel M, Tzivoni D, Behar S, Zahger D, Hod H, Hasdai D, et al. Contemporary treatment and adherence to guidelines in women and men with acute coronary syndromes. BMJ. Elsevier Ireland Ltd; 2008 Dec 17;131(1):97–104. 3. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). American Heart Journal. 2009 Jan;157(1):141–8. 4. Pelletier R, Humphries KH, Shimony A, Bacon SL, Lavoie KL, Rabi D, et al. Sex-related differences in access to care among patients with premature acute coronary syndrome. Canadian Medical Association Journal. 2014 Mar 17. 5. Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. N Engl J Med [Internet]. 1999 Feb 25;340(8):618–26. Available from: http://pubget.com/site/paper/10029647?institution=harvard.edu 6. Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med. 2013 Nov 11;173(20):1863–71. 7. Abramson JL, Veledar E, Weintraub WS, Vaccarino V. Association between gender and In-Hospital mortality after percutaneous coronary intervention according to age. The American Journal of Cardiology. 2003 Apr;91(8):968–71. The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 - Comment #1:
The authors have shown that women are 15% less likely than men to undergo coronary angiography within 60 days from admission for an ACS. Similar but less pronounced differences were found for subsequent revascularization, The cumulative incidence for revascularization within 60 days had an adjusted HR of 0.93 (0.90-0.96).

There are some points that deserve more information and/ or discussion.

(1) The paper confirms that in women, normal/non-significant CAD is highly prevalent. Women with chest pain, whether it is acute coronary syndromes or otherwise are not as often represented in the catheterization laboratory as men. However, the different twist to this manuscript is that when they are represented in the catheterization laboratory, they have the same aggressive interventional as the men who undergo cardiac catheterization. To me, that's the main message of this manuscript, and I would suggest repackaging some of the discussion and citations on this issue.

Reviewer #1 - Our Comment #1:
We agree with the Reviewer that it is a reassuring finding that women and men undergo revascularization to a similar extent following diagnostic coronary angiography (DCA) – especially those patients with extensive coronary artery disease (CAD). Yet, it is also very interesting that women are still 15% less likely to undergo DCA than men when presenting with acute coronary syndromes (ACS) – a difference that has not changed despite extensive, national efforts. In our opinion, this is the most surprising finding that merits further investigation. However, we have added a paragraph to the Interpretation section concerning our finding of differences in extent of CAD in women and men (page 16, line 14) as suggested by the Reviewer.

Reviewer #1 - Comment #2:
(2) The other point is that perhaps aggressive invasive management of the patients not referred to the catheterization laboratory would decrease cardiovascular endpoints. However, that's speculation, since there are no data contained in this manuscript that address that issue. Does this apply to those patients having STEMI or non-STACS? In the manuscript we have data on the entire cohort of patients.
I suggest separating the cohort of patients with STEMI from those with non-STACS, as guideline driven recommendations for coronary angiography, and PCI are quite different for STEMI and non-STACS.

Reviewer #1 - Our Comment #2:
We fully agree with the Reviewer that a stratification of the ACS cohort into patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment acute coronary syndrome (NSTE-ACS) would be interesting in the context of separate guidelines for these two clinical entities. However, the diagnoses of STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) have not been properly validated in the Danish National Patient Register. Therefore, in order to prevent potential misclassification and subsequently biased results, we decided to report our results for the entire ACS cohort. Furthermore, ESC guidelines recommend that an urgent DCA be performed in STEMI patients, while only moderate-to-high risk NSTE-ACS patients (biomarker-positive and/or ST-segment deviations) should undergo accelerated DCA within 72 hours. We addressed this issue by analyzing DCAs at 1, 3 and 60 days (Table 1, page 26, and Table 2, page 28) and in a sensitivity analysis, as stated in the Results section (page 13, line 1), where we excluded all patients with unstable angina pectoris (UAP), thus only focusing on patients diagnosed with myocardial infarction (MI) and made similar findings. Thus, our results did not seem noticeably affected by the presence of low-risk ACS patients in the study cohort.

Reviewer #1 - Comment #3:
(3) Methods and results: more details are needed for Model 4 (adjustment for extent of coronary disease), which is a critical issue in the study.

Reviewer #1 - Our Comment #3:
We agree with the Reviewer that Model 4 adjusting for extent of CAD in rates of revascularization is a

vital analysis. We have added the following description to the methods section to clarify the details regarding the model:

Page 10, line 16, deleted text:
We performed sequential adjustments for explanatory variables as specified in the results section.

Page 10, line 16, inserted text:
We applied a basic Cox regression model with sequential adjustments for age, year of admission, prior revascularization, concomitant heart disease (cardiac arrhythmia, heart failure, pulmonary oedema, and cardiogenic shock), and concomitant comorbidity (cancer, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes with complications, acute renal failure, and chronic renal failure). In the analyses on diagnostic coronary angiography, we performed additional adjustments for demographic characteristics including distance from place of residence to the nearest hospital with cardiac catheterization facilities, income, level of education, and cohabitation status. Similarly, we adjusted for extent of coronary artery disease in the analyses of revascularization.

Reviewer #1 - Comment #4:
(4) Discussion and conclusions: the authors state that “the question, of whether a differing invasive approach in women and men represents a clinically appropriate strategy, an overuse of cardiac catheterization in men or an actual underuse in women, needs to be addressed adequately”. You, therefore, indicate that findings suggest that an increase in catheterization rates in women would have certainly increased the number of patients with obstructive coronary disease being identified, but whether this may have produced improved outcomes is uncertain. I agree. For this reasons, I suggest you report separately the data for STEMI and non-STACS, and also the time to cath in STEMI. Rapid medical intervention is essential to the successful treatment of patients with STEMI because PCI greatly reduces the risk of arrhythmias and death.

Reviewer #1 - Our Comment #4:
We are pleased to hear that the Reviewer agrees with our conclusions. As the Reviewer correctly points out, we simply do not know the coronary anatomy and potential pathology among the ACS patients not undergoing DCA. Some patients in this subgroup – with a high proportion of women – might have significant coronary artery stenoses eligible for revascularization. Prior studies suggest that ACS patients, who do not undergo cardiac catheterization, is heterogeneous but consists mainly of elderly high-risk patients (Hvelplund et al. J Invasive Cardiol. 2012;24(1):19-24). Also, RCTs have demonstrated a similar distribution of coronary artery disease as demonstrated in our study, suggesting that an increased utilization of DCA would result in a concordant increase in the number of patients with obstructive coronary disease being identified and thus eligible for reperfusion therapy (O’Donoghue et al. JAMA. 2008;300(1):71-80). However, studies are needed to address this issue of how sex-related disparities in invasive approach affect clinical outcomes.
Please refer to Comment #2 above (Page 2) for the STEMI vs. NSTE-ACS issue. Regarding symptom-to-catheterization time, this pre-hospital information is unfortunately not available from the Danish National Patient Register.

Reviewer #2 – Comment #1:
In this research paper the authors use data linkage, between established validated national disease registries and administrative datasets, to explore gender differences in the management of patients presenting with acute coronary syndrome throughout Denmark over a 7 year period.

They demonstrate differences in pre-event characteristics between men and women; differences in the proportion of men and women admitted to differing types of hospital in the early management of

their coronary events; differences in the use of diagnostic coronary angiography; differences in the angiographic extent of coronary disease; and differences in subsequent revascularisation. They show that despite these various differences there is no difference in outcome (when outcome is expressed as a 60-day fatality rate). This important point – no difference in outcome despite clear differences in process – should appear in the abstract.

Reviewer #2 – Comment #1:
We thank the Reviewer for a thorough and constructive review. We agree with the Reviewer that the finding of a similar adjusted mortality in women and men despite evident differences in the invasive handling are interesting and important. We have added the following sentence to the abstract:

Page 2, line 14, inserted text:
Mortality rates were similar for both sexes.

Reviewer #2 – Comment #2:
Interestingly during the period studied, changes in the uptake of diagnostic angiography and revascularisation were similar in men and women so there was no apparent "narrowing" of the gender difference.

Strengths & Weaknesses
In common with other registry research, the authors point to limitations related to unmeasured potential confounders that may (partly) explain the gender differences. Categorical variables (e.g. heart failure: yes/no) tend to be recorded in such registries, rather than grades of variable (e.g. severity of chronic kidney disease). Most large registries have significant amounts of missing data in the dataset (which contains multiple items for each individual case). It is unclear how such missing data was addressed in this particular study.

Reviewer #2 – Comment #2:
We agree with the Reviewer that a more in depth description of our handling of missing data is imperative. Hence, we have added the following sentence to the methods section:

Page 10, line 24, inserted text:
Missing data were excluded from the Cox regression models, but sensitivity analyses including missing data as a separate level were performed to assess the influence on our estimates (see Supplementary material).

Reviewer #2 – Comment #3:
The analysis appears reasonable. And the strengths and limitations of the study are well-presented with good contextual introduction and a well written discussion.

The major strength is the use of "big data"/data linkage for a complete nation over a prolonged period of time.

I agree with the authors that it is unfortunate that no distinction can be made between ST elevation myocardial infarction and non-ST elevation MI – but this is a weakness of the chosen ICD coding system.

Discussion & Questions
It is stated that men tend to live further away from hospitals with cardiac catheter facility than women, yet are more likely to be admitted directly to such hospitals. Some of this, I suppose, may relate to an increased proportion of patients with ST elevation being transferred directly to a PCI centre. However, the relevant distance is calculated using the patient's home address and this may not be the same as

their location at the time of onset of symptoms. It's possible that more men (given the age ranges) are at a place of work during the onset of symptoms and therefore could be closer to a catheter facility at the onset of the event than older women on their own at home.

Reviewer #2 – Comment #3:
This is a reasonable thought presented by the Reviewer. In order to address it, we performed a subgroup analysis of patients less than 70 years of age (working age) demonstrating a similar pattern. Significantly more men than women were admitted directly to an invasive heart centre (46% vs. 41%, p<0.001). However, we cannot rule out that the higher prevalence of STEMI in men observed in prior studies may explain this difference.

Reviewer #2 – Comment #4:
There is no calculation, or description, of the time of onset of symptoms and delays to hospitalisation following onset of symptoms. I assume that there is no obvious gender difference, with increased delay from onset of symptoms to admission to hospital in female patients. Occasionally (in the UK at least) patients experience symptoms of their index event many hours (or even >24 hr) before alerting the medical services, and urgent angiography is probably less important in these cases of delay. It is also very interesting, if I understand the findings correctly, that only 34 patients (from almost 60,000) died on the day of admission. This seems a very small proportion. I'm assuming this is more to do with coding issues and qualification for entering the acute coronary syndrome registry than it is the natural history of coronary disease.

Reviewer #2 – Comment #4:
This is a very important point made by the Reviewer. An extensive review of the statistical output identified the source of these skewed numbers. Apparently, patients discharged on the day of admission were excluded before patients who died upon admission causing a misclassification. We have corrected the numbers as stated below. Furthermore, the Danish National Patient Register only contains information on hospitalized patients. Hence, pre-hospital deaths were not recorded. Data on time of onset of symptoms were not available to us, which of course should be noted as a limitation. We have modified the study strengths and weaknesses section to clarify this point:

Page 11, line 19, deleted text:
2 033 patients were <30 or >90 years of age, 4 399 patients were discharged on the day of admission, and 34 patients died on the day of admission leaving 52 565 patients for analysis.

Page 11, line 19, inserted text:
1 035 patients died on the day of admission, 1 953 patients were <30 or >90 years of age, and 3 478 patients were discharged on the day of hospitalization.

Page 15, line 3, deleted text:
Information on core clinical variables such as cardiac biomarkers, electrocardiographic findings, or left ventricular ejection fraction was not available to us.

Page 15, line 3, inserted text:
Information on core clinical variables such as time of onset of symptoms, cardiac biomarkers, electrocardiographic findings, or left ventricular ejection fraction was not available to us; neither was pre-hospital data or out-hospital deaths.

Reviewer #2 – Comment #5:
Is there any evidence that pre-hospital triage, including ECG analysis of the ST segment, is performed more frequently in men than in women in Denmark? It has been suggested elsewhere that ambulance paramedics are less likely to perform ECG recordings in female patients than in males,

and this could lead to more accurate diagnosis and preferential transfer to 'invasive' hospitals for men compared with women.

Reviewer #2 – Comment #5:
This is a very important perspective offered by the Reviewer. No direct comparison between women and men in terms of pre-hospital ECG has been performed in Denmark. A recent study on system-delays in patients transferred for primary PCI suggests that only 25% of patients field-triaged with STEMI are women, and that women may have longer system-delays (Terkelsen et al. JAMA. 2010;304(7):763-771). Therefore, we cannot rule out that any differences in the pre-hospital setting have affected "downstream" investigations and treatments. We have added the following sentence to the study strengths and weaknesses section to elaborate on this point:

Page 15, line 3, inserted text:
Information on core clinical variables such as time of onset of symptoms, cardiac biomarkers, electrocardiographic findings, or left ventricular ejection fraction was not available to us; neither was pre-hospital data or out-hospital deaths.

Reviewer #2 – Comment #6:
With respect to diagnosis, the paper could reference the recent BMJ publication from the group in Edinburgh suggesting that Troponin estimation should have a different (lower) cut point for women than for men [though what effect this would have on the main message (that men and women are managed differently) is unclear].

Reviewer #2 – Comment #6:
We have included the suggested publication (Shah et al. BMJ. 2015;350:g7873) in the Interpretation section.

Reviewer #2 – Comment #7:
It would be useful to have some more discussion as to the frequency of unobstructed coronary arteries in this group of patients with acute coronary syndrome. What does this say about diagnosis, pathophysiology and management that so many more women than men going forward for angiography have unobstructed coronary arteries?

Reviewer #2 – Comment #7:
We agree with the reviewer that the finding of a relatively high prevalence of unobstructed coronary arteries in women compared to men hospitalized with ACS is intriguing. We have included a short elaboration on this finding in the Interpretation section:

Page 16, line 8, inserted text:
In the subgroup of patients undergoing coronary angiography non-obstructive coronary artery disease was found in 22% of women; more than twice as frequent as in men. This finding is consistent with prior studies [28,31] and has been attributed to sex-related differences in the aetiology of MI with e.g. coronary artery spasms, rupture or erosion of eccentric plaques, and Takotsubo syndrome being more frequent in women [32,33]. On the other hand, recent data also suggest that a sex-specific diagnostic threshold for MI using high sensitivity troponins could reclassify women at an increased risk of reinfarction or death who would otherwise be missed using conventional cut-off values [34]. Hence, the relatively high prevalence of unobstructed coronary arteries in women versus men undergoing DCA may reflect a differing aetiology rather than an exaggerated incorrect use of the MI diagnosis in women.

Reviewer #3 – Comment #1:
As regards ethics: Participant consent is not commented and I presume it was not asked for in this retrospective registry study as the authors claim no ethical approval was needed in spite of merging several data bases. Declaration of Helsinki is not mentioned.

As regards study design: The study population, registries and statistics are described properly in the manuscript and the discussion is informative and well balanced - but as the author themselves touch upon - the question whether there exist an inappropriate sex difference in the use of coronary angiography and subsequent revascularization cannot be answered by using this type of registries. Anyhow the findings are still interesting and merits publication after revision as it indicates the need of more studies addressing this question.

Background
Since decades it is known that men and women differ in several aspects when falling ill into ACS. Women are older with higher co-morbidity, have more often UAP and non-obstructive disease but less often STEMI. In NSTE ACS, more solid evidence of an early invasive approach has been found in men, but among high-risk patients, also women benefit from such a strategy. A sex difference in the use of invasive procedures has been shown in plenty of ACS studies, but if temporal trends have changed according to new knowledge would be of interest to explore.

The aim with the present study was to investigate trends in sex differences in the use of invasive coronary procedures in Danish ACS patients 2005 to 2011. The cohort included patients aged 30-90 years with a first-time diagnosis of MI or UAP in the Danish National Patient Registry. Data on co-morbidities was taken from the same registry. Data on invasive procedures was taken from the Danish Heart Registry containing data on all coronary angiography and PCI procedures since 2000. Also other registries were used collecting information about vital and socioeconomic status. The main finding was a 15% less chance of DCA within 60 days in women adjusting for age, co-morbidities, admission year, prior revascularization, distance to PCI-hospital and socioeconomic status. Adjustment for type of ACS (MI or UAP) was not done, but the authors claim that a sensitive analysis on only MI patients showed similar results. No interaction between sex and year of admission was found. Among patients with 2- or 3-vessel disease no difference in subsequent revascularization was found, whereas among patients with 1-vessels disease women had 8 % lower chance of revascularization after multivariable adjustment.

Reviewer #3 – Comment #1:
We thank the Reviewer for taking the time and interest to review our manuscript. We are pleased that the Reviewer finds our manuscript appropriate for further consideration.

Reviewer #3 – Comment #2:
- A major limitation is the inability of discrimination between STEMI and NSTEMI/NSTE ACS in combination with lack of important clinical and angiographic data. The mixture of UAP, NSTEMI and STEMI is problematic because of the well-known sex difference in type of ACS mentioned, but also as the benefit of an early invasive strategy in NSTE ACS differ between the sexes, and thus adjusting for a risk score in this subset of ACS patients would have made the results more solid. In this study, as MI is a more robust diagnosis than UAP (the authors state that the positive predictive value for MI was clearly higher than for ACS in the used registry), I think only MI should have been the inclusion criteria, or at least the results should be stratified for type of ACS.

Reviewer #3 – Comment #2:
We fully agree with the Reviewer that the inability to discriminate between STEMI and NSTE-ACS is an important limitation of this study. Please refer to our previous comment to Reviewer #1 (Our Comment #2) on page 2 for a detailed explanation.

Reviewer #3 – Comment #3:
- No patient with a diagnosis of ACS should be discharge on the admission day. According to the authors this was done in 7% (4399/59031 patients). In the same way 1-day mortality of 0,0006% (34/59031) is very low. This raises questions about the quality on the registry and merits an explanation.

Reviewer #3 – Comment #4:
Please refer to Our Comment #4 (Reviewer #2) on page 6 for an account on the numbers above. In terms of the quality of the registries, the Danish registries have been extensively validated. As described in the Design and data collection section the sensitivity, specificity, and predictive values of the ICD-10 codes for AMI range from 90-95%, although the positive predictive value for ACS is 80%. We addressed this in the sensitivity analysis excluding patients with unstable angina pectoris (UAP) as described on page 13, line 1 in the Results section.

Reviewer #3 – Comment #4:
- Age is a vital confounder in these types of studies and it is important how this variable is handled in the multivariable analyses. In the present study age was categorised into 10-year intervals and included in the multivariable analyses as a category variable. I would like an explanation why age was not handled as a continuous variable in 1-year steps, possible after some form of transformation if needed. What was the result if age was handled as suggested?

Reviewer #3 – Comment #4:
We agree with the Reviewer that age is a vital confounder in all comparative studies. The choice of including age as a factor categorised into 10-year interval was based on extensive tests performed during the building of our final Cox regression models. In practical terms we sequentially tested three models including age as a continuous, a squared, and a 6-levelled factor variable against each other using a log-likelihood ratio test. We found the model including factor variable to be superior to the continuous model. There were no noticeable differences between the estimates obtained with the squared or the factor Cox models (hazard ratio: 0.861 versus 0.854).

Reviewer #3 – Comment #5:
- Outcome measure regarding DCA: Coronary angiography for STEMI should be performed immediately and in NSTEMI within a few days, i.e. the 60 day time limit is questionable. Comparing DCA within 1 day between genders is problematic when no data on MI subtype is available as men have STEMI more often than women. I would suggest DCA during index hospitalization is the main outcome measure, or if not possible, within 1 week.

Reviewer #3 – Comment #5:
The Reviewer correctly points out that in a modern setting most patients presenting with acute myocardial infarction - be it STEMI or NSTEMI - undergo diagnostic coronary angiography within a few days. Yet, guidelines for NSTE-ACS recommend a conservative approach to low-risk patients, who may be referred to outpatient stress-test to investigate for inducible ischemia. Thus, in order to capture these patients in our study cohort as well, we decided to use a primary outcome of diagnostic coronary angiography within 60 days. Furthermore, we sought to ensure external comparability of our results, as prior Danish register-based studies have applied the same definition of outcome (Hvelplund et al. Eur Heart J. 2010 Mar;31(6):684-90 / Gustafsson et al. Open Heart. 2015 Feb 6;2(1):e000165). We have added in-hospital rates of diagnostic coronary angiography and revascularization the Supplementary materials section.

Reviewer #3 – Comment #6:
- Outcome measure regarding revascularization: In 15% of the patients undergoing coronary

angiography, the extent of coronary disease was not known. Probably a higher extent of women than men had non-obstructive disease also in this sub-cohort. Examining possible sex-differences in revascularization in patients undergoing DCA is only meaningful in the sub-cohort where significant coronary lesions were found and analyses should therefor be restricted to that sub-cohort, adjusting for extent of CAD. In my opinion Table 4 can be omitted and replaced by explored data from Figure 3, with added information of ingoing variables in the multivariable models.

Reviewer #3 – Comment #6:
We have moved Table 4 to the Supplementary materials section and added information on model adjustments to Figure 3, as suggested by the Reviewer.

Reviewer #3 – Comment #7:
- As the scope of the whole study is development over time in the sex-differences of use of invasive coronary procedures I would have preferred showing the time trends in more illustrative way, such as showing time trends or stratifying the cohort on inclusion year (or 2-years together) instead of just using an interaction term.

Reviewer #3 – Comment #7:
We would like to draw the Reviewer's attention to Figures 1b and 2b graphically demonstrating the cumulative incidence curves stratified by time-period. These figures also show no interaction between sex and time-period (although unadjusted), as the curves for women and men fail to narrow over time. We have added a reference to these figures following the statement of no interaction between sex and year of admission.

Reviewer #3 – Comment #8:
- Important confounders are missing such as data on renal function and possible anemia. The risk of bleeding and complications due to the invasive procedure are higher in women.

Reviewer #3 – Comment #8:
We agree with the Reviewer that it would be valuable to have information on renal function and anemia. However, our primary source of data was the Danish National Patient Register, which, unfortunately, does not contain information on clinical variables. We have stated this lack of core clinical variables (page 15, line 3) Study strengths and weaknesses, and included considerations regarding the increased risk of peri-procedural complications including bleedings in the discussion section (page 16, line 4).

Reviewer #3 – Comment #9:
- Data on ad-hoc PCI is missing.

Reviewer #3 – Comment #9:
We acknowledge that no data on ad-hoc PCI are presented in the current manuscript. Although, ad-hoc PCI is the current standard in Denmark, this information was not available to us.

Reviewer #3 – Comment #10:
- Kaplan-Meyer curves could be omitted as unadjusted data says very little about pure gender differences.

Reviewer #3 – Comment #10:
Please refer to Comment #7 on page 11 for an explanation for the use of the cumulative incidence curves.

Reviewer #3 – Comment #11:

- Inconsequent presenting of p<0.001 in the tables, see table 1 and 3. For some variables the p-value is probably missing.

Reviewer #3 – Comment #11:
All p-values are available in the tables. The p-values, which the Reviewer refers to, are stated above the numbers and frequencies in the p-value column, as they represent a Chi-squared test for a 2xk-table. We have added a note under the tables clarifying this point.

Reviewer #3 – Comment #12:
Summary
If a lower chance for women to undergo DCA among high-risk NSTE ACS patients within index hospitalisation could be shown with no change over time, this would be an important finding. In STEMI we have used the Swedish quality registry for MI care, SWEDEHEART, in order to explore temporal trends of reperfusion and other evidenced-based therapy, finding a gender gap that did not diminish during the studied time period (Sederholm Lawesson, BMJ Open, 2012). In the present study a registry including only information on diagnoses of hospitalizes patients was used and thus important clinical and angiographic data is missing. Thus, the finding of a gender gap in the use of DCA among unselected hospitalized ACS patients is interesting but the question whether this gap is inadequate or not merits further studies.

Reviewer #3 – Comment #12:
We are pleased to hear that the Reviewer agrees with our conclusions. We fully acknowledge the shortcomings of our study and have addressed them extensively in the discussion section.

Reviewer #4 – Comment #1:
This study addresses a health policy question of significant salience. Despite the importance of the scientific question, the strength of the database, the overall quality of the writing the authors should address several important limitations. The following comments and requests for clarification are offered with the goal of strengthening the manuscript.
Summary: This is a contemporary Danish registry population-based study on trends in the invasive therapies and diagnostics among patients with ACS. 2005-2011. The main outcome of interest is sex disparities in the receipt of diagnostic cardiac catheterization and revascularization procedures (PCI and CABG) in setting of acute coronary syndromes (STEMI, NSTEMI, UA). The impetus for this study was motivated by recent public health and health care system interventions in Denmark aimed at improving access to streamlined and evidence-based care and a public awareness campaign specifically dedicated at reducing previously identified sex-disparities in care of cardiac patients. Data sources included the Danish National Patient Registry, Danish Heart Registry, Danish National Prescription Registry, Danish Register of Causes of Death and Statistics Denmark.
Overall the data source is excellent, the methods appear to be quite sound and the writing very good. The discussion is thoughtful with a good understanding of the state of the current literature with respect to sex disparities in ACS. The authors are quite insightful about the limitations of the study and measured in their conclusions which is a strength. My major criticism of this study is that overall in its current form adds little to the current state of knowledge. I feel that given the strength of their data source and methodology, more could have been done in this regard. In my opinion, the issue of disparity in the receipt of DCA or revascularization alone without investigation of clinical outcomes significantly limits the salience of the analysis. Mortality data is available in their data source, yet it was only investigated briefly in an age-adjusted analysis and not in the context of use of these invasive cardiac procedures. Additionally, it is implied that the investigation of these invasive cardiac procedures represents a measure of the quality of care received between the sexes, and alone this may be incomplete. For example, data are presented on medication use on admission for men and

women and the receipt of evidence-based therapies in the context of ACS may be another useful measure of quality of care. It would be an interesting addition to the analysis to investigate the use of evidence-based medical therapies between the sexes for ACS on discharge if available. Previous work has shown sex disparities in this context (1-3) and, if found in this cohort, would strengthen the argument for the presence of inappropriate gender bias in the care received between the sexes.
The authors correctly point out that appropriateness of use of these invasive procedures is a critical factor that requires further investigation. Unfortunately, as the authors point out there are limitations in the data that prevent this analysis. To this end, I believe the most interesting aspect of this study was the investigation of effect modification by extent of coronary artery disease on receipt of revascularization (Figure 3). It is known that women have less obstructive CAD, and in this study the bulk of the disparities in revascularization appear to be entirely appropriate as they are largely among subjects with no significant stenosis thus, likely not representative of unwanted gender bias.
Other factors worth considering in their interpretation/discussion: Gender bias among physicians (4,5), differences in presentation with ACS (6) patient preferences for invasive procedures vs. conservative management, and age-related effect modification by sex (7).

Reviewer #4 – Comment #2:
Abstract:
Concise and well written. If space allows, I would suggest inclusion of the results of the effect modification by extent of coronary artery disease on revascularization analysis as an important finding of this analysis. This analysis would need to be motivated briefly as well.

Reviewer #4 – Comment #2:
We thank the Reviewer for the positive feedback on our abstract. Unfortunately, there is not enough space in the abstract to include a comment on the effect modification without disturbing the overall balance and conciseness.

Reviewer #4 – Comment #3:
Introduction:
The introduction is well written and clearly motivates the impetus behind this analysis explaining recent policy and care changes in Denmark.
• It would be helpful to include more information about the Danish Heart Foundation public awareness campaign on sex-related differences and perhaps a reference. If this campaign was specifically designed to reduce known sex disparities readers may appreciate a better understanding of what modalities it used and if any portion of it was focused at healthcare providers who are often those who make treatment and triage decisions for different therapies and transfers to major hospitals when appropriate.

Reviewer #4 – Comment #3:
We thank the Reviewer for the kind words regarding the introduction. We have added the sentences below to clarify the details of the Danish Heart Foundation public awareness campaign. Unfortunately, only a report on the campaign written in Danish is available (http://boccawired.ipapercms.dk/Hjerteforeningen/Rapportermm/Elskhjertetresultater2012).

Page 5, line 19, inserted text:
The campaign included advertisement on multiple media platforms using Danish female celebrities as leading figures. Also, a total of €2.14 million were allocated to 15 national research projects concerning women and cardiovascular disease.

Reviewer #4 – Comment #4:
• Also, there is an inherent presumption that the impetus to reduce sex-related disparities in treatment is to also improve the outcomes of care, however sex-differences in clinical outcomes after ACS are

not mentioned (mentioned above in global summary).

Reviewer #4 – Comment #4:
This is an important point made by the Reviewer. We fully agree that the ultimate goal of reducing sex-related differences in treatment would be to improve prognosis. We did not perform this analysis for two main reasons. First, we wanted to keep the manuscript short, concise, and with a clear message. If we were to assess the impact of differential invasive treatment on e.g. death, this would require sophisticated statistical tools (i.e. instrumental variable analysis) or extensive stratified calculations as invasive treatment acts as a mediating factor between exposure (sex) and outcome (death). We have, however, provided crude and adjusted mortality rates in the Supplementary materials section to accommodate the interested reader.

Reviewer #4 – Comment #5:
Methods:
The data sources are very good and truly population-based (Entirety of Denmark). Good explanation of definitions used for primary diagnosis in Denmark (important for context). The authors used validated definitions of AMI within the data sources used. They also used validated invasive cardiac procedures and prescriptions. All strengths.
Specific comments:
• Page 6: Please provide more information about data from Statistics Denmark: “Information on emigration, income, level of education, cohabitation status, and distance to hospitals with cardiac catheterization facilities were collected from Statistics Denmark.” Is this information individually reported or aggregated area-level data from a national census?

Reviewer #4 – Comment #5:
We thank the Reviewer for the kind words regarding our data sources. All data used in this study are patient-level data. We have made the following correction to the methods section in order to clarify this:

Page 7, line 3, deleted text:
Information on emigration, income, level of education,…

Page 7, line 3, inserted text:
Patient-level data on emigration, income, level of education,…

Reviewer #4 – Comment #6:
• Page 7, paragraph 2: Exclusions are reasonable however I don’t believe that those that die on the same day of admission may all be necessarily ineligible for cardiac catheterization. For example, a severe ACS may go for an emergency procedure and have a fatal arrhythmia on the table in the cardiac catheterization laboratory, but not be included in this study. As only 34 patients of the entire cohort were excluded in this way I doubt that their inclusion will affect the study results and may improve validity by avoiding this criticism.

Reviewer #4 – Comment #6:
We agree that the scenario the Reviewer presents here is a possibility. However, given the administrative nature of the data, it is perhaps even more likely that patients who died upon hospitalization did not have a certain diagnosis at the time of death, but were diagnosed with MI anyway. This would cause misclassification and eventually bias our estimates. Hence, we have not included these patients in our analyses.

Reviewer #4 – Comment #7:
• Page 7, paragraph 3: “Only a minor group was self directed or referred to emergency departments

from their general practitioner." Please clarify how many patients this represents (proportion) and if possible, whether there is a gender disparity in this patient population.

Reviewer #4 – Comment #7:
We acknowledge that these numbers would be of interest, but they are not available for the study cohort. The above statement is based on a prior study from a Danish region, which estimated that only 7% of STEMI patients are self-presenters (Schoos et al. Eur Heart J: Acute Cardiovasc Care. 2012;1(3):200-209).

Reviewer #4 – Comment #8:
• Page 8, paragraph 2: The outcomes measures are reasonable except Table 1 (page 24) lists revascularization rates for within 1, 3, and 60 days and the methods only mentions revascularization within 60 days.

Reviewer #4 – Comment #8:
We have added a sentence to the methods section in order to clarify that 1-, 3-, and 60-day DCA rates were analysed.

Page 8, line 11, inserted text:
Cardiac catheterizations performed within 1 and 3 days corresponding to early and delayed procedures were also assessed.

Reviewer #4 – Comment #9:
• Age adjusted 60-day mortality rates are presented in the results section (page 10, paragraph 4) but this analysis is not introduced in the methods section. Additionally why this outcome was only adjusted for age is not justified in the methods section? This is especially confusing in light of the citation of the Ontario MI prediction rule for 30-day and 1-year mortality (page 9, paragraph 1) as justification for inclusion of comorbidities in the analysis for the receipt of coronary angiography.

Reviewer #4 – Comment #9:
We presented the age-adjusted 60-day mortality showing no significant differences between women and men to justify that women were not simply less invasively investigated and treated due to a higher mortality. We have changed the sentence in the results section as shown below to prevent any ambiguities:

Page 11, line 20, deleted text:
There were no significant gender differences in age-adjusted 60-day mortality with a hazard ratio 1.04 (0.98-1.11).

Page 11, line 20, inserted text:
Adjusted 60-day mortality was similar between women and men (see Supplementary material).

Reviewer #4 – Comment #10:
• Page 8, paragraph 3: Please explain why age was categorized into 10 year intervals and included as a categorical variable. I don't understand the value of this as age is always a very important predictor of both treatment and outcomes. By categorizing this variable there is a loss of information and statistical power.

Reviewer #4 – Comment #10:
Please refer to Comment #4 for Reviewer #3 on page 10 for a detailed explanation.

Reviewer #4 – Comment #11:

• Socioeconomic status by net annual family income needs to be clarified. Is this census-derived area-level family income or individual household reported? Additionally the categorization into low, medium and high needs to be defined in a monetary figure and justified.

Reviewer #4 – Comment #11:
Data on net annual family income and level of education are patient-level. The data represents the net annual family income after taxes of the household in which each individual patient resides. We have added a reference justifying our use of the above categorization and the following sentence to the methods section:

Page 8, line 20, deleted text:
Socioeconomic status was assessed by annual net family (low, medium or high), highest achieved educational level (short, medium or long), and cohabitation status.

Page 8, line 20, inserted text:
Socioeconomic status was assessed by annual net family income after taxes calculated separately for patients ≤65 and >65 years of age in order to account for any changes following retirement, highest achieved educational level, and cohabitation status [20,21].

Page 8, line 22, inserted text:
Annual net family income was divided into tertiles of low (≤65 years: < €34 639 / >65 years: < €27 132), medium (€34 639 to €57 633 / €27 132 to €44 512), or high (> €57 633 / > €44 512) income. Highest achieved educational level was divided into three groups according to duration of training: short (a maximum of 9 years of school), medium (grammar school or vocational training), or long (university degree).

Reviewer #4 – Comment #12:
• Highest educational level achieved similarly needs to be clarified and defined (ie. years of education or level of education in each category)

Reviewer #4 – Comment #12:
Please refer to Comment #11 above.

Reviewer #4 – Comment #13:
• What geographical program was used to perform the distance calculations between patients' homes and nearest hospital? Please include in the methods section.

Reviewer #4 – Comment #13:
All distances between each patients home address as of 1 January the year of admission and cardiac catheterization hospitals when travelling by road were calculated by Statistics Denmark using GIS (Geographical Information System) software. We have modified the following sentence in the methods section to clarify this:

Page 7, line 5, inserted text:
…who also performed all distance calculations using GIS (Geographical Information System) software.

Reviewer #4 – Comment #14:
• The number of hospital transfers is included in Table 1 (page 24) but not mentioned in the methods section. Please clarify how this variable was calculated

Reviewer #4 – Comment #14:

We thank the Reviewer for pointing out this shortage. We have added a definition of the hospital transfer variable to the methods section:

Page 9, line 19, inserted text:
Hospital transfers
Transfer of patients between hospitals were identified using an algorithm that combined unique hospital identifiers, dates of admission, and dates of discharge into one total index hospitalization provided that dates were overlapping.

Reviewer #4 – Comment #15:
• Page 8, paragraph 4: "Diagnoses of heart failure, cardiogenic shock, dysrhythmia and pulmonary oedema indicated the severity of heart disease". While this is reasonable, heart failure can be a pre-existing chronic comorbidity. Was the presence of CHF on presentation as a marker of severity of ACS distinguished from CHF as a comorbidity?

Reviewer #4 – Comment #15:
This is a very important issue indicated by the Reviewer. We were not able to discriminate between CHF as a presenting feature of ACS and CHF as an 'isolated' comorbidity. Our definitions of concomitant heart disease and comorbidity relied solely on ICD-10 coding – not clinical variables. Hence, we cannot with any certainty distinguish between these two clinical entities.

Reviewer #4 – Comment #16:
• In the adjusted models presented in Table 2, it is not clear if these above markers of severity of ACS are included in the adjustment. "comorbidity" is listed but these markers of ACS severity are not comorbidities and if included in the models should be clearly stated.

Reviewer #4 – Comment #16:
We have expanded the description of comorbidities in Table 2 as suggested.

Reviewer #4 – Comment #17:
• Page 9, paragraph 1: Why was revascularization within 3-years of the index event only included in the analysis? The justification provided is that this may influence the decision to pursue invasive examination, but presumably the receipt of a CABG 4-years before the index event would be as likely to influence these decisions.

Reviewer #4 – Comment #17:
We fully agree with the Reviewer that revascularization within 4 years of index hospitalization would be just as likely as revascularization within 3 years to affect the decision to perform a new cardiac catheterization. The reason why we used prior revascularization within 3 years was that we only had information available on cardiac procedures since 2002. As our cohort was defined from 1 January, 2005 to 2 November 2011, this leaves only 3 years of prior observation in terms of cardiac procedures.

Reviewer #4 – Comment #18:
• Statistical Analysis: How was the clustering effect modelled in their cox models? What correlation structures were assumed and what statistical procedures used?

Reviewer #4 – Comment #18:
As described in the methods section (page 10, line 14) we estimated hazard ratios using Cox regression models applying robust estimation under the assumption that observations correlated within individual hospitals. We used the cluster() option in the stcox procedure in Stata Statistics/Data analysis, MP 13.0 (StataCorp, Texas; USA) which estimates robust standard errors applying the

Huber-White sandwich estimator.

Reviewer #4 – Comment #19:
Results:
• It is not clear why age-adjusted 60-day mortality was chosen to be presented instead of fully adjusted mortality outcomes.

Reviewer #4 – Comment #19:
We agree with the Reviewer that it is not sufficiently clarified in the manuscript, why age-adjusted 60-day mortality was chosen. The main reason for including this gender comparison of 60-day mortality was to show the reader that mortality did not differ between women and men, thus justifying the use of Cox regression models when comparing cardiac procedures. We only adjusted for age to keep the model simple, yet adjusting for the main confounder of age. As stated previously we have provided additional crude and adjusted mortality data in the Supplemental materials section.

Reviewer #4 – Comment #20:
• Spelling out the cumulative incidences from Figure 1a does not add any information not already presented in the unadjusted rates of each invasive procedure in the sentence above. Stating the unadjusted HR's would suffice.

Reviewer #4 – Comment #20:
We thank the Reviewer for pointing out this redundancy in the results section. We have removed the cumulative incidences from the text:

Page 12, line 16, deleted text:
The cumulative incidence for examination with DCA within 60 days was higher for men (0.78) than women (0.66) (Figure 1a) resulting in an unadjusted female-male hazard ratio (HR) of 0.71 (0.68-0.74) with similar results at day 0-1, day 2-3, and the following 56 days (Table 2).

Page 12, line 20, inserted text:
The higher cumulative incidence of examination with DCA in men compared to women (Figure 1a) resulted in an unadjusted female-male hazard ratio (HR) of 0.71 (0.68-0.74) with similar results at day 0-1, day 2-3, and the following 56 days (Table 2).

Page 13, line 13, deleted text:
The cumulative incidence for revascularization when examined with DCA within 60 days was higher for men (0.78) than for women (0.63) (Figure 2a) yielding an unadjusted HR of 0.66 (0.64-0.69) (Table 4).

Page 13, line 13, inserted text:
The higher cumulative incidence for revascularization when examined with DCA within 60 days in men compared to women (Figure 2a) yielded an unadjusted HR of 0.66 (0.64-0.69).

Reviewer #4 – Comment #21:
• Page 12, line 42: "female gender was associated with slightly lower rate of PCI". It would be helpful for the reader to clarify that these are adjusted rates again

Reviewer #4 – Comment #21:
We have rephrased the sentence above to emphasize that adjusted estimates are reported:

Page 13, line 18, inserted text:
…in the fully adjusted models,…

Reviewer #4 – Comment #22:
• The last section of the results that discusses the interaction between coronary artery disease and receipt of invasive procedures is likely the most interesting part of this analysis and novel. I would elaborate on this section somewhat. Also, this analysis feels like it comes out of nowhere as it was never motivated in the introduction as to why you think this should be the case. This analysis was not explained in the methods section either, thus contributing to my feelings of surprise. I suggest doing both

Reviewer #4 – Comment #22:
We agree with the Reviewer that the interaction between sex and extent of CAD when analysing the risk of revascularization is thrilling. However, this association was discovered when testing the model assumptions. Hence, we find it somewhat misleading to classify this analysis as a pre-specified one. We have already specified in the Statistical analysis section that "Model assumptions – interactions, non-informative censoring, and proportional hazards – were found valid unless otherwise indicated." We believe that this brief motivation suffices.

Reviewer #4 – Comment #23:
• Lastly, the unadjusted rates of revascularization by extent of coronary artery disease should likely be presented. The adjusted OR of 0.47 for revascularization among women compared to men is a large effect size. It would be helpful to know what the rates are that are associated with the adjusted and unadjusted results presented in Figure 3.

Reviewer #4 – Comment #23:
We would like to draw the Reviewer's attention to the third column in Figure 3 entitled "Any revascularization at 60 days, No. (%)" The numbers in parentheses indicate crude rates of revascularization, and the numbers demonstrate the relative weight of each group.

Reviewer #4 – Comment #24:
• Table 2 and Table 3 should be reversed in order. Table 2 presents the adjusted results and should come after Table 3 with unadjusted comparisons and description of coronary artery disease severity

Reviewer #4 – Comment #24:
We fully comprehend the logic of this comment. However, we find that the current order of Tables 2 and 3 is most suitable for two reasons: 1) The current order reflects the order in which the tables are cited, and 2) Table 2 includes analyses on the entire study cohort (N=52 565), while Table 3 only includes patients examined by DCA (N=39 677) – a subgroup investigated at a later stage in the analyses. Hence, we have kept the current order of the above tables.

Reviewer #4 – Comment #25:
• Figures: Please list the covariates that are included in the adjusted models in a footnote below the Figure 3.

Reviewer #4 – Comment #25:
We have added a list of variables included in the adjusted models displayed in Figure 3 as suggested by the Reviewer.

Reviewer #4 – Comment #26:
• Table 2 has a footnote that explains model 4 has a smaller sample size (n=48 609). This is not explained in the methods section. Missing data, if significant should be addressed in the methods and how it was handled, as it can add important selection biases.

Reviewer #4 – Comment #26:
Please refer to Reviewer #2, Comment #2 on page 5 for our reply regarding missing data.

Reviewer #4 – Comment #27:
Discussion:
• In the limitations section in page 14, when discussing the lack of core clinical variables as a potential source of unmeasured confounding. I would also include that the use of these variables would allow for a validated severity score of ACS at presentation and would allow a mechanism to assess appropriateness of DCA between the sexes.

Reviewer #4 – Comment #27:
We have added the following sentence to the discussion section to accommodate the Reviewer's request:

Page 15, line 6, inserted text:
Inclusion of clinical variables in future studies would allow for a validated severity score of ACS upon presentation providing a tool to assess appropriateness of DCA use between sexes.

Reviewer #4 – Comment #28:
• The authors should concede that the lack of clinical outcomes in this analysis is a major limitation in their ability to interpret the sex disparity in the receipt of invasive cardiac procedures that they have identified.

Reviewer #4 – Comment #28:
Please refer to Comment #30 on page 22 for our reply.

Reviewer #4 – Comment #29:
• In the interpretation of the results implicit gender bias is not discussed as a possibility to explain the disparities identified, although this has been identified in previous studies. Additionally, there was no mention of the differences in symptom presentation between men and women with ACS as a potential explanation that may effect physician decision making as well.

Reviewer #4 – Comment #29:
We fully agree with the Reviewer that the aspects presented above are important. However, in the Interpretation section (page 15, line 17) we refer to a study by Vaccarino et al. (N Engl J Med 2005;353:671-82), who demonstrated persistent sex-related differences in rates of coronary angiography among AMI patients deemed ideal candidates for cardiac catheterization. This study suggests that differences in clinical presentation alone cannot explain sex-related differences.

Reviewer #4 – Comment #30:
• The final sentence of the discussion raises the question about clinical appropriateness and the need to investigate overuse/underuse. This implies understanding the clinical outcomes resulting from these disparities and should be clarified.

Reviewer #4 – Comment #30:
We have rephrased the final sentence of the discussion section to clarify the importance of reaching an understanding of clinical outcomes resulting from sex-related differences in invasive management of ACS patients:

Page 17, line 9, deleted text:
More specifically, the question, of whether a differing invasive approach in women and men represents a clinically appropriate strategy, an overuse of cardiac catheterization in men or an actual

underuse in women, needs to be addressed adequately.

Page 17, line 9, inserted text:
More specifically, the questions, of whether a differing invasive approach in women and men represents a clinically appropriate strategy, an overuse of cardiac catheterization in men or an actual underuse in women, and how this disparity affects clinical outcomes, need to be addressed adequately.

Reviewer #4 – Comment #31:
Minor Points:
• Typo: Page 11, line 33: “to omen”

Reviewer #4 – Comment #31:
We have corrected the typo as shown below.

Page 12, line 16, deleted text:
… to omen.

Page 12, line 16, inserted text:
… to men.

Reviewer #4 – Comment #32:
• Page 11, paragraph 1: “Despite living a bit further from hospitals”. Minor point, colloquial English should be edited

Reviewer #4 – Comment #32:
We have corrected the colloquial error as shown below.

Page 12, line 8, deleted text:
Despite living a bit further from hospitals with cardiac catheterization facilities…

Page 12, line 8, inserted text:
Despite living slightly further from hospitals with cardiac catheterization facilities…

Reviewer #4 – Comment #33:
• Typo: page 12, line 26: “toomen”

Reviewer #4 – Comment #33:
We have corrected the typo as shown below.

Page 13, line 12, deleted text:
… toomen ...

Page 13, line 12, inserted text:
… to men ...

Reviewer #4 – References:
1. Opotowsky AR, McWilliams JM, Cannon CP. Gender Differences in Aspirin use Among Adults With Coronary Heart Disease in the United States. J GEN INTERN MED. 2007 Jan 9;22(1):55–61.
2. Moriel M, Tzivoni D, Behar S, Zahger D, Hod H, Hasdai D, et al. Contemporary treatment and adherence to guidelines in women and men with acute coronary syndromes. BMJ. Elsevier Ireland Ltd; 2008 Dec 17;131(1):97–104.

3. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). American Heart Journal. 2009 Jan;157(1):141–8.
4. Pelletier R, Humphries KH, Shimony A, Bacon SL, Lavoie KL, Rabi D, et al. Sex-related differences in access to care among patients with premature acute coronary syndrome. Canadian Medical Association Journal. 2014 Mar 17.
5. Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. N Engl J Med [Internet]. 1999 Feb 25;340(8):618–26. Available from: http://pubget.com/site/paper/10029647?institution=harvard.edu
6. Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med. 2013 Nov 11;173(20):1863–71.
7. Abramson JL, Veledar E, Weintraub WS, Vaccarino V. Association between gender and In-Hospital mortality after percutaneous coronary intervention according to age. The American Journal of Cardiology. 2003 Apr;91(8):968–71.

VERSION 2 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna italy
REVIEW RETURNED	06-Apr-2015

GENERAL COMMENTS	Suggestion 1# Women with chest pain, whether it is acute coronary syndromes or otherwise are not as often represented in the catheterization laboratory as men. However, the different twist to this manuscript is that when they are represented in the catheterization laboratory, they have the same aggressive interventional as the men who undergo cardiac catheterization. To me, that's the main message of this manuscript, and I would suggest repackaging some of the discussion and citations on this issue. Reply Yet, it is also very interesting that women are still 15% less likely to undergo DCA than men when presenting with acute coronary syndromes (ACS) – a difference that has not changed despite extensive, national efforts New comment of the reviewer The authors did not address the issue. Did the authors conclude that their model suggests potential for application into clinical practice? The fact that women are less likely to undergo DCA is well known and does not need further studies. Moreover unlike men, women presenting with low-risk NSTE-ACS do not seem to benefit from an early invasive approach (O'Donoghue M JAMA), which is now recognized even by guidelines. Unfortunately there is no distinction that can be made between ST elevation MI and non-ST elevation MI, which is the major fault of the study. Suggestion 2# I suggest separating the cohort of patients with STEMI from those with non-STACS, as guideline driven recommendations for coronary angiography, and PCI are quite different for STEMI and non-STACS. Reply

The diagnoses of STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) have not been properly validated in the Danish National Patient Register.
In a sensitivity analysis, as stated in the Results section (page 13, line 1), where we excluded all patients with unstable angina pectoris (UAP), thus only focusing on patients diagnosed with myocardial infarction (MI) and made similar findings. Thus, our results did not seem noticeably affected by the presence of low-risk ACS patients in the study cohort

New comment of the reviewer

The authors did not address the issue, Perhaps, this could have been possible. Indeed, Terkelsen, et al made distinction between ST elevation MI and non-ST elevation MI and recently published in JAMA 2010 such data. This study was based on public medical databases that cover the entire population of Western Denmark (approximately 3 million, corresponding to 55% of the Danish population). Data on mortality were obtained from The Danish Civil Registration System, which has recorded changes in vital status of the entire Danish population since 1968. Vital status is updated daily. Baseline characteristics and other covariates were derived from the Danish Civil Registration System, the WDHR, and the National Registry of Patients. One of the authors (J S Jensen) of the current manuscript was coauthors of the above mentioned paper. Furthermore, there is no substantial changes in the manuscript (and tables), even if the authors acknowledged to have excluded at least those patients with UA. The reviewer believes that excluding UA and limiting the analysis to those patients with DCA on day 1 (more than 19,000) may reduce bias at acceptable levels. Propensity analysis may also be of help if the study includes patients with both ST elevation MI and non-ST elevation MI (BMJ Open. 2013 Apr 24;3(4). pii: e002559. doi: 10.1136/bmjopen-2013-002559. Print 2013).

Suggestion 3#
Methods and results: more details are needed for Model 4 (adjustment for extent of coronary disease), which is a critical issue in the study.

Reply

We applied a basic Cox regression model with sequential adjustments for age, year of admission, prior revascularization, concomitant heart disease (cardiac arrhythmia, heart failure, pulmonary oedema, and cardiogenic shock), and concomitant comorbidity (cancer, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes with complications, acute renal failure, and chronic renal failure). Similarly, we adjusted for extent of coronary artery disease in the analyses of revascularization

New comment of the reviewer

The authors partially addressed the reviewer's concern. What does it mean heart failure? Does it mean history of heart failure or heart failure ad admission? Pulmonary edema seems to overlap such information, and it is an important prognosticator of adverse outcome and less catheterization use (Eur Heart J. 2011 Jun;32(11):1337-44. doi: 10.1093/eurheartj/ehr027. Epub 2011 Mar 7). This applies as well to cardiogenic shock.

	Furthermore age was not handled as a continuous variable, and this would be important in the regression analyses of this study. Medications prior to index admission should be included as well in the regression model, as they may influence outcomes, clinical presentation and therefore clinical decision making on catheterization in non-ST elevation MI. Conversely, medications at admission are nor reported, but they may do so as well. Baseline characteristics and other covariates may be derived from the Danish Civil Registration System. Suggestion 4# I suggest you report separately the data for STEMI and non-STACS, and also the time to cath in STEMI Reply Regarding symptom-to-catheterization time, this pre-hospital information is unfortunately not available from the Danish National Patient Register New comment of the reviewer This is an important fault in the data of the manuscript. Indeed, recent work has shown that physicians are less likely to perform ECG recordings in women than in men after an anginal attack. If STEMI women are mostly latecomers they should not receive primary PCI, which may largely justify the data of the manuscript. As above mentioned Terkelsen, et al (JAMA 2010) published data on the “System Delay and Mortality Among Patients With STEMI Treated With Primary PCI” These data are available in the Western Denmark Heart Registry, and this may be of help. The WDHR serves as a regional data source to the Danish Heart Registry, which also contains data from Eastern Denmark and thus is responsible for the national monitoring of cardiac intervention quality.

REVIEWER	Clive Weston College of Medicine Swansea University, Swansea United Kingdom
REVIEW RETURNED	26-Mar-2015

GENERAL COMMENTS	I believe that the authors have carefully considered the comments of the reviewers and have responded in a reasonable and constructive way - providing explanations and making amendments that strengthen the original submission

REVIEWER	Sofia Sederholm Lawesson Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Sweden
REVIEW RETURNED	11-Apr-2015

GENERAL COMMENTS	The authors have responded well to the reviewer questions and comments and changed the manuscript accordingly.

REVIEWER	Gabriel Fabreau University of Calgary, Canada
REVIEW RETURNED	17-Apr-2015

GENERAL COMMENTS	I applaud the authors on their hard work and response to the many revisions requested. I agree that the paper is suitable for publication. I still have one minor difficulty with the paper as written however. In my comments (Reviewer 4 Comment #22). I was concerned about the interaction analysis summarized in Figure 3 as a very important finding from this study that was neither introduced or well explained in the methods. This finding then features prominently in both the results section and now in paragraphs 2 and 3 of the Interpretation section. I appreciate the authors' response with regards to these finding being somewhat surprising and not pre-specified; however, higher degree of non-obstructive CAD in women has been well described (as referenced by the authors) and not unexpected. I still feel that this interaction testing by sex needs to be explained somewhat further in the methods section. Surely the interaction testing by sex performed in the model construction was not completely random as it feels to me that is currently implied in the methods. I feel that this finding is an important one in this study and if the authors feel that the methods is sufficiently explained (which I do not) then the fact that these findings were unexpected should at least be explained in the discussion section. As it reads to me in the current interpretation section, it feels like these findings were an intended investigation and discussed as such. "We agree with the Reviewer that the interaction between sex and extent of CAD when analysing the risk of revascularization is thrilling. However, this association was discovered when testing the model assumptions. Hence, we find it somewhat misleading to classify this analysis as a pre-specified one. We have already specified in the Statistical analysis section that “Model assumptions – interactions, non-informative censoring, and proportional hazards – were found valid unless otherwise indicated.” We believe that this brief motivation suffices."

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 - Comment #1:
I believe that the authors have carefully considered the comments of the reviewers and have responded in a reasonable and constructive way - providing explanations and making amendments that strengthen the original submission.

Reviewer #1 – Our Comment #1:
We thank the Reviewer for taking the time to review our manuscript. The Reviewer’s suggestions and comments have definitely improved the manuscript.

Reviewer #2 - Comment #1:
Suggestion 1#
Women with chest pain, whether it is acute coronary syndromes or otherwise are not as often represented in the catheterization laboratory as men. However, the different twist to this manuscript is

that when they are represented in the catheterization laboratory, they have the same aggressive interventional as the men who undergo cardiac catheterization. To me, that's the main message of this manuscript, and I would suggest repackaging some of the discussion and citations on this issue.

Reply
Yet, it is also very interesting that women are still 15% less likely to undergo DCA than men when presenting with acute coronary syndromes (ACS) – a difference that has not changed despite extensive, national efforts

New comment of the reviewer
The authors did not address the issue. Did the authors conclude that their model suggests potential for application into clinical practice? The fact that women are less likely to undergo DCA is well known and does not need further studies. Moreover unlike men, women presenting with low-risk NSTE-ACS do not seem to benefit from an early invasive approach (O'Donoghue M JAMA), which is now recognized even by guidelines. Unfortunately there is no distinction that can be made between ST elevation MI and non-ST elevation MI, which is the major fault of the study.

Reviewer #2 – Our Comment #1:
We thank the Reviewer for taking the time to review our revised manuscript. Regarding the Reviewer's first question of the potential clinical application of our model, it is unclear what model the Reviewer is in fact referring to – the statistical regression models or the models underlying the nationwide initiatives presented in the Introduction section. Hence, we will address both perspectives.

1) Statistical models: We did not build our regression models with a view to predict outcomes or apply in a clinical setting. Our regression models were built exclusively for confounder control to obtain as unbiased estimates for the association between sex and invasive procedures as our data allowed.

2) National initiatives: We make no inferences regarding any effects of the national fast-track protocols for NSTE-ACS, the extensive pre-hospital EMS triaging, or the public awareness campaign focusing on sex-related differences in cardiovascular diseases, as we have no direct measure available. We merely conclude that despite extensive national measures the sex-related differences in the use of cardiac catheterization have not attenuated.
In terms of the lack of ability to discriminate between STEMI and NSTEMI we fully acknowledge this as a major limitation of our study. We have pointed this out in the text for the "Strengths and limitations of this study"-box. In order to accommodate the concerns raised by the Reviewer, we have added the sentence below to the Study strengths and weaknesses section.

Page 16, line 7, inserted text:
We were unable to discriminate between STEMI and NSTEMI, as the ICD-10 diagnoses for these sub diagnoses have not been validated in the Danish National Patient Register.

In terms of the Reviewer's perspective, that the association between sex and use of diagnostic coronary angiography is well-established and require no further investigation, the authors will have to disagree. We find it imperative to continuously reassess these discrepancies in access to guideline-recommended therapy using temporal analyses. As we describe in the Introduction section, several national initiatives have been implemented to ensure equal access to invasive cardiac examinations in Denmark, which could have affected the association. Hence, we find that this is more than enough impetus for our study. Had the findings been different and the sex-related differences been attenuated, the initiatives described above would be of potential interest to other countries as well.

Reviewer #2 - Comment #2:
Suggestion 2#

I suggest separating the cohort of patients with STEMI from those with non-STACS, as guideline driven recommendations for coronary angiography, and PCI are quite different for STEMI and non-STACS.

Reply
The diagnoses of STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) have not been properly validated in the Danish National Patient Register.
In a sensitivity analysis, as stated in the Results section (page 13, line 1), where we excluded all patients with unstable angina pectoris (UAP), thus only focusing on patients diagnosed with myocardial infarction (MI) and made similar findings. Thus, our results did not seem noticeably affected by the presence of low-risk ACS patients in the study cohort

New comment of the reviewer
The authors did not address the issue, Perhaps, this could have been possible. Indeed, Terkelsen, et al made distinction between ST elevation MI and non-ST elevation MI and recently published in JAMA 2010 such data. This study was based on public medical databases that cover the entire population of Western Denmark (approximately 3 million, corresponding to 55% of the Danish population). Data on mortality were obtained from The Danish Civil Registration System, which has recorded changes in vital status of the entire Danish population since 1968. Vital status is updated daily. Baseline characteristics and other covariates were derived from the Danish Civil Registration System, the WDHR, and the National Registry of Patients. One of the authors (J S Jensen) of the current manuscript was coauthors of the above mentioned paper. Furthermore, there is no substantial changes in the manuscript (and tables), even if the authors acknowledged to have excluded at least those patients with UA. The reviewer believes that excluding UA and limiting the analysis to those patients with DCA on day 1 (more than 19,000) may reduce bias at acceptable levels. Propensity analysis may also be of help if the study includes patients with both ST elevation MI and non-ST elevation MI (BMJ Open. 2013 Apr 24;3(4). pii: e002559. doi: 10.1136/bmjopen-2013-002559. Print 2013).

Reviewer #2 – Our Comment #2:
We agree with the Reviewer that the lack of distinction between STEMI and NSTEMI is a major limitation of our study. The Reviewer understandably draws our attention to a prior Danish study on STEMI patients from Western Denmark (Terkelsen et al. JAMA. 2010;304(7):763-771). Although the study by Terkelsen et al. presented several important clinical characteristics not available in the national registries, the study was performed on a highly selected group of patients (Figure 2, page 766). Patients were eligible only if they were admitted for primary PCI. Hence, the study includes patients selected for reperfusion therapy. In our study, as we point out in the “Strengths and weaknesses of the study”-box, we wanted to focus on an unselected cohort including all incident hospitalizations for ACS in Denmark regardless of selection for invasive cardiac procedures. This, we believe, prevents the risk of differential misclassification and ensures external validity of our findings, although limiting the degree of detail in our data. We hope that the Reviewer will find our answer adequate and will appreciate our careful considerations of sample selection versus level of detail.
In terms of the Reviewer’s suggestion of excluding UAP patients and patients receiving DCA beyond day 1 to limit bias, it is unclear what bias the Reviewer is referring to. Does the Reviewer want to assess STEMI patients only? This is very contrary to our aim of assessing sex-related differences in the invasive diagnostic-therapeutic cascade in an unselected national ACS cohort. In Table 2 (page 28) we present cumulative as well as time-stratified Cox regression analyses including a separate estimate for ACS patients undergoing DCA within 1 day of admission – a subgroup of patients most likely to consist of mainly STEMI patients and those with severe hemodynamic instability. We later state (page 14, line 3) that excluding UAP patients did not change our estimates. Hence, it is unclear what the Reviewer wish to gain with his suggested analysis that is not already outlined in the manuscript.

Although, propensity score analyses offer many benefits, we refrained from their use in our analyses. These methods are based on the assumption of no unmeasured confounders. As clinical presentation with STEMI versus NSTEMI is a very plausible strong confounder that is unknown in our data, propensity score analysis would not solve the underlying issue of being able to discriminate between STEMI and NSTEMI. Given our large sample size, high number of events, and the lack of core clinical variables, we consider a well-specified Cox regression model as being equivalent to a propensity score based approach. We hope that the Reviewer agrees.

Reviewer #2 - Comment #3:
Suggestion 3#
Methods and results: more details are needed for Model 4 (adjustment for extent of coronary disease), which is a critical issue in the study.

Reply
We applied a basic Cox regression model with sequential adjustments for age, year of admission, prior revascularization, concomitant heart disease (cardiac arrhythmia, heart failure, pulmonary oedema, and cardiogenic shock), and concomitant comorbidity (cancer, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes with complications, acute renal failure, and chronic renal failure). Similarly, we adjusted for extent of coronary artery disease in the analyses of revascularization

New comment of the reviewer
The authors partially addressed the reviewer's concern. What does it mean heart failure? Does it mean history of heart failure or heart failure ad admission? Pulmonary edema seems to overlap such information, and it is an important prognosticator of adverse outcome and less catheterization use (Eur Heart J. 2011 Jun;32(11):1337-44. doi: 10.1093/eurheartj/ehr027. Epub 2011 Mar 7). This applies as well to cardiogenic shock.
Furthermore age was not handled as a continuous variable, and this would be important in the regression analyses of this study. Medications prior to index admission should be included as well in the regression model, as they may influence outcomes, clinical presentation and therefore clinical decision making on catheterization in non-ST elevation MI. Conversely, medications at admission are nor reported, but they may do so as well. Baseline characteristics and other covariates may be derived from the Danish Civil Registration System.

Reviewer #2 – Our Comment #3:
As specified in the Explanatory variables subsection (page 10, line 8-17) comorbidity was defined using ICD-10 coding in accordance with the Ontario MI mortality predictive rule (So et al. BMC Health Serv Res 2006;6:161). All diagnoses made within one year prior to and during the index admission were included. Thus, if a patient had been hospitalized with a primary or secondary diagnosis contained within the Ontario predictive rule, this patient was considered as suffering from this particular comorbid condition.
Regarding the modelling of age in our Cox regressions, we refer to the argumentation provided in the prior review-answer to Reviewer #3:
"We agree with the Reviewer that age is a vital confounder in all comparative studies. The choice of including age as a factor categorised into 10-year interval was based on extensive tests performed during the building of our final Cox regression models. In practical terms we sequentially tested three models including age as a continuous, a squared, and a 6-levelled factor variable against each other using a log-likelihood ratio test. We found the model including factor variable to be superior to the continuous model. There were no noticeable differences between the estimates obtained with the squared or the factor Cox models (hazard ratio: 0.861 versus 0.854)."
We fully agree with the Reviewer that usual medications prior to index admission may be important confounders in the sex-invasive examination association – especially among NSTE-ACS patients.

Therefore we have included an additional column in Table 2 adjusting for medication prior to index hospitalization.
Regarding the Reviewer's request for in-hospital medication, these data are not available from the Danish National Patient register – only in-hospital procedures. We recognize that these data would be of interest, but are not able to provide them.
As to the Reviewer's final sentence, the Danish Civil Registration System is a continuously updated historical base register containing individually identifiable information on i.e. address, marital status, vital status, and emigration/immigration status on all Danish citizens. Data from this register have already been extensively used to generate our study cohort and would, in our opinion, not provide any additional information on covariates as suggested by the Reviewer.

Reviewer #2 - Comment #4:
Suggestion 4#
I suggest you report separately the data for STEMI and non-STACS, and also the time to cath in STEMI

Reply
Regarding symptom-to-catheterization time, this pre-hospital information is unfortunately not available from the Danish National Patient Register

New comment of the reviewer
This is an important fault in the data of the manuscript. Indeed, recent work has shown that physicians are less likely to perform ECG recordings in women than in men after an anginal attack. If STEMI women are mostly latecomers they should not receive primary PCI, which may largely justify the data of the manuscript. As above mentioned Terkelsen, et al (JAMA 2010) published data on the "System Delay and Mortality Among Patients With STEMI Treated With Primary PCI" These data are available in the Western Denmark Heart Registry, and this may be of help. The WDHR serves as a regional data source to the Danish Heart Registry, which also contains data from Eastern Denmark and thus is responsible for the national monitoring of cardiac intervention quality.

Reviewer #2 – Our Comment #4:
We fully agree with the Reviewer that data on symptom-to-catheterization time would be of great interest and the lack of these data in our analysis represents an important limitation. We have disclosed this lack of pre-hospital data in the Study strengths and limitations section (Page 16, line 7). We would once again like to refer to the fact that the study by Terkelsen et al. was performed on a selected population of STEMI patients referred for primary PCI. EMS and treatment-delay data were missing in 11.5% (1477/12877) of patients. Hence, the risk of misclassification, when applying these selected data to our unselected cohort, would increase significantly. We hope that the Reviewer shares this view.

Reviewer #3 - Comment #1:
The authors have responded well to the reviewer questions and comments and changed the manuscript accordingly.

Reviewer #3 – Our Comment #1:
We thank the Reviewer for a thorough and constructive review that has indeed strengthened the manuscript significantly.

Reviewer #4 - Comment #1:
I applaud the authors on their hard work and response to the many revisions requested. I agree that the paper is suitable for publication.
I still have one minor difficulty with the paper as written however. In my comments (Reviewer 4 Comment #22). I was concerned about the interaction analysis summarized in Figure 3 as a very important finding from this study that was neither introduced or well explained in the methods. This finding then features prominently in both the results section and now in paragraphs 2 and 3 of the Interpretation section.
I appreciate the authors' response with regards to these finding being somewhat surprising and not pre-specified; however, higher degree of non-obstructive CAD in women has been well described (as referenced by the authors) and not unexpected. I still feel that this interaction testing by sex needs to be explained somewhat further in the methods section. Surely the interaction testing by sex performed in the model construction was not completely random as it feels to me that is currently implied in the methods.
I feel that this finding is an important one in this study and if the authors feel that the methods is sufficiently explained (which I do not) then the fact that these findings were unexpected should at least be explained in the discussion section. As it reads to me in the current interpretation section, it feels like these findings were an intended investigation and discussed as such.

"We agree with the Reviewer that the interaction between sex and extent of CAD when analysing the risk of revascularization is thrilling. However, this association was discovered when testing the model assumptions. Hence, we find it somewhat misleading to classify this analysis as a pre-specified one. We have already specified in the Statistical analysis section that “Model assumptions – interactions, non-informative censoring, and proportional hazards – were found valid unless otherwise indicated.” We believe that this brief motivation suffices."

Reviewer #4 – Our Comment #1:
We thank the Reviewer for his kind words regarding our extensive revision of the manuscript. We fully understand the Reviewer’s concerns regarding the interaction analysis presented in Figure 3 and agree that further justification is merited in the manuscript. As the Reviewer correctly points out, the analysis was not randomly performed. It was performed for two primary reasons: 1) To assess if model assumptions were fulfilled, 2) Ghali et al. have previously presented data from a Canadian cohort of patients with coronary artery disease, who had undergone cardiac catheterization, suggesting that more men with normal, near-normal, one- or two-vessel disease than women are subsequently revascularized (Ghali et al. Ann Internal Med. 2002;136:723-732). Although, our study cohort was less heterogeneous and more contemporary than that of Ghali et al., we found it important to assess this issue in our study. We have added the sentence below to the Statistical analysis section to motivate the interaction analysis.

Page 12, line 1, inserted text:
Motivated by prior findings that severity of coronary artery disease as assessed during cardiac catheterization may affect the use of reperfusion therapy differently in women and men [25], we conducted an interaction analysis between sex and extent of coronary disease.