

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.
<b>AUTHORS</b>	Mårtensson, Solvej; Gyrd-Hansen, Dorte; Prescott, Eva; Andersen, Per; Zwisler, Ann-Dorthe; Osler, Merete

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Jørn Olsen Arhus University, Denmark
<b>REVIEW RETURNED</b>	18-Oct-2013

<b>GENERAL COMMENTS</b>	There is nothing wrong with this paper but it is mainly of interest for those being treated at these hospitals in Denmark. It is descriptive vital statistics.
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<b>REVIEWER</b>	Søren Paaske Johnsen and Tobias Pilgaard Ottosen Department of Clinical Epidemiology Aarhus University Hospital Denmark
<b>REVIEW RETURNED</b>	19-Oct-2013

<b>GENERAL COMMENTS</b>	<p>The investigators examined time trends in invasive examination and time to treatment for patients with first time diagnosis of non-ST-elevation Myocardial infarction (NSTEMI) and unstable angina in the period 2001-2009 in Denmark. The background for this period was a development and implementation of a fixed treatment protocol for these patients in 2009. The study found a significant increase in the proportion of patients receiving coronary angiography (CAG) and percutaneous coronary intervention (PCI) between 2001 and 2009, while the proportion receiving coronary artery bypass graft (CABG) decreased. Furthermore, the proportion of patients receiving early CAG and PCI (i.e., defined as <math>\leq 3</math> days) increased substantially, in particular in the last part of the study period.</p> <p>The topic of the study is clearly of clinical and public health relevance and the manuscript is well-written and easy to follow. The methodology, including the thorough statistical analyses, appears sound and the conclusions made are supported by the presented data. However, the authors could consider the following issues:</p> <p>Major comments:</p> <ul style="list-style-type: none"><li>- Introduction: The authors state that "the purpose of this study is to explore the potential causes of the significant improvement in prognosis by...". However, the study focuses only on use of invasive examination and treatment and does not present analyses linking</li></ul>
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increased use of CAG and PCI with changes in patient outcome, including mortality. The presented study purpose should therefore more accurately reflect the real contents of the study.

- Methods: The main concern with the study is the choice of study period. The study period ends in 2009 and the data is consequently already somewhat old. Since the study is based on existing Danish registries it should be possible to present more updated data when we are now approaching the end of 2013. This issue is of particular importance, since the fixed treatment protocols were only first introduced in 2009 and the full effect of these protocols may therefore not be fully captured in the study. This suspicion is also supported by the substantial increase in the proportion of patients with early CAG and PCI within the last years of the study period.

- Study population: The description of the study population is somewhat short and not entirely clear. Please provide some information about the patients which were excluded since they did not receive a CAG or died within 60 days. They account for more than 1/3 of the population presented and appear to include a large number of patients with an unstable or NSTEMI diagnosis. Please also see comment below concerning the validity of the ACS diagnoses in the National Registry of Patients.

- Discussion:

o It would be relevant with a more in depth discussion about the proportion of patients treated according to the timeframes defined set by the fixed protocol, i.e. NSTEMI CABG patients treated within 7 days decreased from 28.4% in 2001 to 23.0 in 2009, despite the treatment rate was halved.

o The authors argue that the coronary heart disease diagnoses in the National Registry of Patients are of high quality and refer to a previous validation study, which reported a positive predictive value of 98% of a myocardial infarction diagnosis in the Danish National Registry of Patients. However, the validation study only compared diagnoses mentioned in the discharge summaries with diagnoses recorded in the National Registry of Patients and did not validate whether the diagnoses were in fact correct. However, the predictive value of ACS diagnoses in the National Registry of Patients have been examined in another study using detailed clinical information from medical records, including ECGs and biomarker measurements, as reference (Joensen AM et al. J Clin Epidemiol. 2009;62:188-94). The study found that the ACS diagnoses contained in the National Registry of Patients should be used with caution and that the unstable angina diagnosis was particularly troublesome. This limitation should be discussed more thoroughly.

o The large number of patients being excluded from the study due to lack of CAG or death within 60 days combined with the concerns about the validity of NSTEMI/unstable angina diagnoses in the National Registry of Patients leaves some uncertainty as to how the study findings can or should be interpreted. At best the majority of the excluded patients did not really have NSTEMI/unstable angina. However, there is also a possibility, which cannot be excluded based on the presented data, that a substantial number of patients are not treated optimally (i.e., examined and treated to late or not at all). This uncertainty should be better reflected in the Discussion section.

Minor comments:

- Method: The National Prescription Registry is mentioned as a register used for this study, however it is not presented anywhere how and why it is used. Please clarify.

- The use of abbreviations is somewhat inconsistent. Some abbreviations are not written out the first time they are used (e.g.,

	<p>LMCA on page 7), whereas others are used in different versions (e.g., “CAG” and “cag”). Please proof read carefully.</p> <ul style="list-style-type: none"> <li>- Variables: This section is without any presentation of the co-variables. Instead, they are presented under the discussion section. In general, the article could be optimized in its structure, to give a better overview.</li> <li>- Statistical methods: <ul style="list-style-type: none"> <li>o This section could be reduced in length (in particular the description of the basic principles of competing risk).</li> </ul> </li> <li>- Other: The title and objective specifically distinguish between examination and treatment. However, this distinction is not consistently used throughout the article is as CAG often is referred to as treatment (e.g., bottom of page 11 and top of page 13). Please rephrase.</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Name Jørn Olsen

Institution and Country Aarhus University, Denmark

Please state any competing interests or state ‘None declared’: None

There is nothing wrong with this paper but it is mainly of interest for those being treated at these hospitals in Denmark. It is descriptive vital statistics.

Reviewer Name Søren Paaske Johnsen and Tobias Pilgaard Ottosen

Institution and Country Department of Clinical Epidemiology

Aarhus University Hospital

Denmark

Please state any competing interests or state ‘None declared’: None declared

The investigators examined time trends in invasive examination and time to treatment for patients with first time diagnosis of non-ST-elevation Myocardial infarction (NSTEMI) and unstable angina in the period 2001-2009 in Denmark. The background for this period was a development and implementation of a fixed treatment protocol for these patients in 2009. The study found a significant increase in the proportion of patients receiving coronary angiography (CAG) and percutaneous coronary intervention (PCI) between 2001 and 2009, while the proportion receiving coronary artery bypass graft (CABG) decreased. Furthermore, the proportion of patients receiving early CAG and PCI (i.e., defined as  $\leq 3$  days) increased substantially, in particular in the last part of the study period. The topic of the study is clearly of clinical and public health relevance and the manuscript is well-written and easy to follow. The methodology, including the thorough statistical analyses, appears sound and the conclusions made are supported by the presented data. However, the authors could consider the following issues:

Major comments:

1. Introduction: The authors state that “the purpose of this study is to explore the potential causes of the significant improvement in prognosis by...”. However, the study focuses only on use of invasive examination and treatment and does not present analyses linking increased use of CAG and PCI with changes in patient outcome, including mortality. The presented study purpose should therefore more accurately reflect the real contents of the study.

We agree that the wording is not precise enough. We have changed the purpose so we now only speak of investigating a potential explanation (change in time to invasive examination and treatment for patients) and not causes in general. Furthermore we use the word describe instead of investigate, as the later could lead the reader to believe that this is a study on the effects of a change in time to

invasive examination and treatment on the prognosis which is not the case.

We have further reduced the purpose to only focus on changes in time to invasive examination and treatment, which is the primary interest in the paper. This has caused us to also slightly modify the title of the paper.

2. Methods: The main concern with the study is the choice of study period. The study period ends in 2009 and the data is consequently already somewhat old. Since the study is based on existing Danish registries it should be possible to present more updated data when we are now approaching the end of 2013. This issue is of particular importance, since the fixed treatment protocols were only first introduced in 2009 and the full effect of these protocols may therefore not be fully captured in the study. This suspicion is also supported by the substantial increase in the proportion of patients with early CAG and PCI within the last years of the study period.

We agree that more up-to-date data would be very interesting and relevant. It would be possible to have the data updated to 2011 however we don't have the funds to buy additional data from the Danish National Board of Health.

3. Study population: The description of the study population is somewhat short and not entirely clear. Please provide some information about the patients which were excluded since they did not receive a CAG or died within 60 days. They account for more than 1/3 of the population presented and appear to include a large number of patients with an unstable or NSTEMI diagnosis. Please also see comment below concerning the validity of the ACS diagnoses in the National Registry of Patients.

Patients who do not receive a CAG or die within 60 days are not excluded from the analysis; they still contribute with time at risk in both the cumulative incidence curves and the fine-Gray models. However it is correct that there are some problems regarding the validity of the ACS diagnosis in the NPR. Please see detailed answer to question 5.

Discussion:

4. It would be relevant with a more in depth discussion about the proportion of patients treated according to the timeframes defined set by the fixed protocol, i.e. NSTEMI CABG patients treated within 7 days decreased from 28.4% in 2001 to 23.0 in 2009, despite the treatment rate was halved.

It is difficult for us to see what the reviewers are looking for. That the same proportion of patients are treated within 7 days combined with fewer being treated totally could be because more patients are treated with PCI but the patients treated with CABG still wait the same time. It could be a problem of capacity or there simply have not been the same focus on timing of CABG treatment compared to PCI.

5. The authors argue that the coronary heart disease diagnoses in the National Registry of Patients are of high quality and refer to a previous validation study, which reported a positive predictive value of 98% of a myocardial infarction diagnosis in the Danish National Registry of Patients. However, the validation study only compared diagnoses mentioned in the discharge summaries with diagnoses recorded in the National Registry of Patients and did not validate whether the diagnoses were in fact correct. However, the predictive value of ACS diagnoses in the National Registry of Patients have been examined in another study using detailed clinical information from medical records, including ECGs and biomarker measurements, as reference (Joensen AM et al. J Clin Epidemiol. 2009;62:188-94). The study found that the ACS diagnoses contained in the National Registry of Patients should be used with caution and that the unstable angina diagnosis was particularly troublesome. This limitation should be discussed more thoroughly.

We agree that the study is very relevant to our analysis. Thank you for point out this gap in our

references. Based on this information we have reworked our analyses, so we now exclude outpatients and patients where the NSTEMI or Angina diagnosis is not verified in a ward. We have changed the text in the method section adding:

A previous study by Joensen et al. found that the ACS diagnosis registered in the NPR should be used with caution especially the unstable angina diagnosis (12). Joensen et al. recommend restricting the analysis to patients discharged from wards when other validation is not possible. We therefore excluded outpatients (n=2,564) and patients with a NSTEMI or unstable angina diagnosis from an emergency room that was not verified in the subsequent admission (n=11,560) still allowing for a shift from NSTEMI to unstable angina or vice versa. Consequently, the final population consisted of 65,909 patients.

We reran all analyses and changed tables, figures, text and appendix accordingly (notice: track changes in the appendix and for figures made it completely illegible, so this was not used).

This change did not change the main conclusions regarding timing and the fixed treatment protocols, but for unstable angina the CAG examination rate increased substantially.

- The large number of patients being excluded from the study due to lack of CAG or death within 60 days combined with the concerns about the validity of NSTEMI/unstable angina diagnoses in the National Registry of Patients leaves some uncertainty as to how the study findings can or should be interpreted. At best the majority of the excluded patients did not really have NSTEMI/unstable angina. However, there is also a possibility, which cannot be excluded based on the presented data, that a substantial number of patients are not treated optimally (i.e., examined and treated to late or not at all). This uncertainty should be better reflected in the Discussion section.

We have added a paragraph regarding patients who are not treated in the end of the discussion section:

We found that the number of patients receiving the recommended invasive examination and treatment within the recommended time frame increased from 2001 to 2009, however a large group of patients still received no invasive investigation or were treated later than the guideline recommends in 2009. This patient group consists of three possible groups: patients that don't have the disease in question due to lack of validity of data (see later discussion of strengths and weaknesses), patients who are too ill to be treated and patients who receive a less than optimal treatment. The basic idea behind the fixed treatment protocol i.e. same treatment for patients presenting with the same clinical symptoms irrespective of when or where patients come in contact with the health care system should ensure that the latter group is proportionally smaller in 2009 than in 2001. However, there could still be patients who don't receive optimal treatment and unexplained variation between hospitals. Therefore monitoring by health authorities is of great importance.

Regarding interpretation see answer to question 5.

Minor comments:

- Method: The National Prescription Registry is mentioned as a register used for this study, however it is not presented anywhere how and why it is used. Please clarify.

We apologize for this. The National Prescription Registry is not used in the study and we have therefore removed this sentence.

- The use of abbreviations is somewhat inconsistent. Some abbreviations are not written out the first time they are used (e.g., LMCA on page 7), whereas others are used in different versions (e.g., "CAG" and "cag"). Please proof read carefully.

Thank you for pointing this out. We have proof read more carefully

- Variables: This section is without any presentation of the co-variables. Instead, they are presented under the discussion section. In general, the article could be optimized in its structure, to give a better overview.

We have already presented information regarding the variables time to treatment and severity and extent of disease. Further covariates only include age, sex and year of diagnosis. We have added a sentence regarding these variables in this section.

- Statistical methods:

o This section could be reduced in length (in particular the description of the basic principles of competing risk).

We agree that this section is rather long however we believe that presenting the competing risks analysis and the reasons behind is of great importance to avoid misconceptions. Furthermore the paper is well below the word maximum

- Other: The title and objective specifically distinguish between examination and treatment. However, this distinction is not consistently used throughout the article is as CAG often is referred to as treatment (e.g., bottom of page 11 and top of page 13). Please rephrase.

Thank you for pointing this out. We have corrected this however in the statistical analysis part where we describe the competing risks analysis we only mention treatment.

#### **VERSION 2 – REVIEW**

<b>REVIEWER</b>	Søren Paaske Johnsen and Tobias Pilgaard Ottosen Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
<b>REVIEW RETURNED</b>	01-Dec-2013

<b>GENERAL COMMENTS</b>	The authors have responded to our comments in a satisfactory way and the manuscript has been substantially improved. No further comments.
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