Author's response to reviews

Title: Prevalence and prognosis of non-specific chest pain among patients hospitalized for acute coronary syndrome - a systematic literature search

Authors:

Vidar VR Ruddox (vidar.ruddox@siv.no)
Mariann MM Mathisen (mariann.mathisen@kunnskapssenteret.no)
Jan Erik JEO Otterstad (jan.erik.otterstad@siv.no)

Version: 2 Date: 3 April 2012

Author's response to reviews: see over
Ref. Your mail from 8 March 2012, MS 3393790066562188

Incidence and prognosis of non-specific chest pain among patients recruited from consecutive series of hospitalizations for acute coronary syndrome. Vidar VR Ruddox, Mariann MM Mathisen and Jan Erik JEO Otterstad.

Thank you for the review and assessment of this manuscript. We have chosen not to use the track changes function, as it might lead to errors such as double spacing unnoticed by ourselves. Therefore changes in the manuscript are marked with red text. This means that deletions and moved text will not be visible, but should be apparent from this cover letter.

This cover letter will go through the editorial revisions and comments by reviewer 1 and 2 in this order.

Editorial revisions

1. The original figure legend was taken from the text in the figure presented in the PRISMA statement (BMJ 2009; 339: b2535 doi 10.1136/bmj/2435). We have now expanded the text as follows:

   Figure 1. Flow of information obtained from a systematic search of 4 databases (PUBMED, MEDLINE, EMBASE and PsycINFO) with addition of citations identified through other sources, and presentation of full text articles that had been evaluated and excluded for predefined reasons. Abbreviations: ACS = Acute coronary syndrome; NSCP = non-specific chest pain.

2. We have tried, to our best ability, to adhere to the PRISMA guidelines, going systematically through the 27 suggested items as follows:

   Title: This now been changed according to the suggestion put forward by reviewer 1: Prevalence and prognosis of non-specific chest pain among consecutive patients hospitalized for acute coronary syndrome – a systematic literature search

   Abstract: This is slightly shortened to contain the following of the suggested headings: Background, Methods, Results and Conclusions. We did not included data sources, study eligibility criteria, participants and interventions, study appraisal and synthesis methods and implication of key findings since we felt that the abstracts then would be too long. This is similar to our previous systematic review in BMC Medicine (Aune et al. BMC Medicine 2011; 9: 97). The amendments put forward by both reviewers however, have been included

   Introduction: Rationale and Objectives are presented consecutively.

   Methods:

   Protocol and registration: The Research protocol is presented in Appendix I as additional file 1. Registration is not included.
Eligibility criteria, information sources, search, study selection, data collection process and data items are provided consecutively.

**Risk of bias in individual studies:** This has now been moved to and combined with the bias section in the discussion, according to reviewer 1.

**Summary measures:** N.A.

**Synthesis of results:** This is presented under results, following the results of individual studies.

**Risk of bias across studies:** Moved to the discussion section, according to reviewer 1.

**Additional analysis:** Not necessary for this review (see reviewers` comments on no need for further statistics)

**Results:** Presented as in the previous version of the manuscript, but with systematic inclusion of prognostic data, whenever reported, as pointed out by reviewer 1. Table 1 has been kept unchanged except from the addition of reference 20 according to the additional search performed in PubMed (Epub ahead of print, see the Method section and the addition of this search protocol in Appendix I. We have provided additional information on mortality for “ACS/high risk” patients in the text.

**Discussion:** Now includes summary of evidence, risk of bias in the review, Limitations and Conclusions, all modified according to the two reviewers (see below)

**Fundings:** As in the previous version

**List of Abbreviations, Competing interest and Authors’ contributions** are also provided although not described in the PRISMA checklist.

3. It is now stated in the title that this is a systematic review.

**Reviewer 1:** Mohammed Justin Zaman

**Major compulsory revisions**

1. **Abstract methods:** Now contains the following:

   *This is a systematic literature search where 3 databases were searched from 1990 onwards to 14 NOV 2011. In addition, one database was searched for Epub ahead of print per 24 MAR 2012*

2. **Introduction:** The objectives section is now rewritten: *The premise of the review is to obtain information on the prevalence and prognosis of NSCP in comparison with patients with ACS. Such information might be of importance in the optimal management of patients with NSCP, since there are no guidelines for this large and important group.*
3. **Risk of bias:** All concerning bias has now been moved to a separate heading in the discussion, underlining the importance of selection bias in the heterogeneous groups of patients included in the various studies.

4. **Prevalence not incidence:** We completely agree to this correction and have consistently used prevalence in the title and throughout the paper.

5. **Expansion of results and eliminating them from the discussion:**

   a. We have moved the first para of the discussion into “summary of results”.

   b. We have now included data on prognosis and readmission for all included articles in the section “Background information on the studies presented in table 1”.

   **The comparative prognosis between those with ACS and those with NSCP should be brought out:**

   We have made some efforts to accomplish this important suggestion.

   i. In the Introduction, second para we have introduced such a comparison

   *The premise of the review is to obtain information regarding the prevalence and prognosis of NSCP in comparison with patients with ACS.*

   ii. In the Methods section, we have added as the last inclusion criterion: *Although desirable, studies without follow-up data on “ACS/high risk” patients could be included, provided all other inclusion criteria were met.*

   iii. In the results section we have included information provided for mortality and readmission data for patients with NSCP, and of mortality data for patients with “ACS/high risk” wherever they have been presented. Regretfully, only one of the selected studies reported the one-year readmission rate for chest pain among “ACS/high risk” patients (ref. 12), and this is included under study characteristics and in the summary of results sections.

6. **Conclusions:** Such patients understandably might be more concerned about pain that is musculoskeletal and that might not worry others with a history of CHD.

   This valuable point has been included in the discussion, forth para, and has been discussed to more detail in the same para, including reference to the reviewer’s own study (now reference 23), as recommended. Furthermore, we have cited ref. 28, recently published in the European Heart Journal, as we feel that this paper stresses important points of psychiatric disorders in the management of the NSCP group.

7. **Title:** This has been changed as suggested, see editorial revisions #2.
8. **The prognosis of NSCP compared to those with ACS:** Please, note the changes as described under reviewer 1, comment #5. We do hope that the clarity and coherence of the manuscript has been improved.

**Minor Essential Revisions:**

The writing in this revised version has once more been amended by Mathew McGee, professional proofreader born and raised in UK.

**Reviewer 2: Guy Eslick**

**Could the authors please expand their literature search by including PubMed as one of the search engines:**

We have included PubMed as the forth search engine utilized. We did not include PubMed in the first version on already printed articles, since this database in principle reflects Ovid Medline. The exception is that PubMed also includes references being “ahead of print”. As described in the methods section, we included a search in PubMed for Epub articles ahead of print per 24 MAR 2012.

This search provided us with 9 references published as Epub articles ahead of print. The search history is added in Appendix A. This search resulted in inclusion of 1 article (ref. 20), which is included in table 1. The resulting overall figures are adjusted in the Abstract and the Results section. The remainder 8 full size articles were excluded, and listed in Appendix B (5 due to selection criteria and 3 to the lack of definition of “ACS/high risk”).

**Could the authors please expand their terminology and include non-cardiac/noncardiac chest pain and atypical chest pain:**

Line 4 of the search strategy:

```plaintext
4 (chest burn or ((cardiac or **chest** or heart or thorax or thoracic) adj2 pain) or ((cardiac or angina) adj2 syndrome x) or (microvascular adj2 angina) or ((suspected or potential or subsequent* or recurrent or repeat* or previous*) adj2 (acute coronary syndrome* or acs or acute myocardial infarct* or ami or stroke*))).tw.
```

Which means that the above mentioned phrases are covered by the search. We have looked into the consequences of including non-cardiac/noncardiac chest pain and atypical chest pain. From the two columns below, you will see that such an inclusion does not change the number of citations returned:

<table>
<thead>
<tr>
<th>Results</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: (chest burn or ((cardiac or chest or heart or thorax or thoracic) adj2 pain) or ((cardiac or angina) adj2 syndrome x) or (microvascular adj2 angina) or ((suspected or potential or subsequent* or recurrent or repeat* or previous*) adj2 (acute coronary syndrome* or acs or acute myocardial infarct* or ami or stroke*))).tw.</td>
<td>26782</td>
</tr>
<tr>
<td>B: (((noncardiac or non-cardiac or atypical) adj chest pain) or chest burn or ((cardiac or chest or heart or thorax or thoracic) adj2 pain) or ((cardiac or angina) adj2 syndrome x) or (microvascular adj2 angina) or ((suspected or potential or subsequent* or recurrent or repeat* or previous*) adj2 (acute coronary syndrome* or acs or acute myocardial infarct* or ami or stroke*))).tw.</td>
<td>26782</td>
</tr>
</tbody>
</table>
The reason why the excellent article by Eslick and Talley (Neurogastroenterol Motil 2008; 20: 989-997) was not included in the search was that we originally had tried to limit it to patients who are readmitted. If we exclude that part of the search as demonstrated below, the return is well above 1 million citations, and Eslick’s article will be included:

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chest Pain/</td>
<td>7994</td>
</tr>
<tr>
<td>2</td>
<td>Microvascular Angina/</td>
<td>802</td>
</tr>
<tr>
<td>3</td>
<td>(chest burn or ((cardiac or chest or heart or thorax or thoracic) adj2 pain) or ((cardiac or angina) adj2 syndrome x) or (microvascular adj2 angina) or ((suspected or potential or subsequent* or recurrent or repeat* or previous*) adj2 (acute coronary syndrome* or acs or acute myocardial infarct* or ami or stroke*)))tw.</td>
<td>28190</td>
</tr>
<tr>
<td>4</td>
<td>or/1-3</td>
<td>31155</td>
</tr>
<tr>
<td>5</td>
<td>etiology.fs.</td>
<td>1870034</td>
</tr>
<tr>
<td>6</td>
<td>incidence/ or prevalence/</td>
<td>291744</td>
</tr>
<tr>
<td>7</td>
<td>Cross-Sectional Studies/</td>
<td>135852</td>
</tr>
<tr>
<td>8</td>
<td>(incidence* or prevalence* or epidemiol*).tw.</td>
<td>894142</td>
</tr>
<tr>
<td>9</td>
<td>epidemiology.fs.</td>
<td>1022248</td>
</tr>
<tr>
<td>10</td>
<td>or/6-9</td>
<td>1621941</td>
</tr>
<tr>
<td>11</td>
<td>&quot;Outcome Assessment (Health Care)&quot;/</td>
<td>40965</td>
</tr>
<tr>
<td>12</td>
<td>fatal outcome/ or hospital mortality/ or survival rate/</td>
<td>167238</td>
</tr>
<tr>
<td>13</td>
<td>treatment outcome/</td>
<td>510306</td>
</tr>
<tr>
<td>14</td>
<td>(cardiac adj2 outcome*).tw.</td>
<td>2302</td>
</tr>
<tr>
<td>15</td>
<td>mortality.fs.</td>
<td>360443</td>
</tr>
<tr>
<td>16</td>
<td>or/11-15</td>
<td>923075</td>
</tr>
<tr>
<td>17</td>
<td>cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/</td>
<td>1152659</td>
</tr>
<tr>
<td>18</td>
<td>((prospective or retrospective) adj3 stud*).tw.</td>
<td>281062</td>
</tr>
<tr>
<td>19</td>
<td>(consecutiv* adj5 patient*).tw.</td>
<td>128569</td>
</tr>
<tr>
<td>20</td>
<td>or/17-19</td>
<td>1281795</td>
</tr>
</tbody>
</table>

Accordingly, we have kept the search unchanged. Eslick and Talley’s paper is categorized as “additional citations” in Appendix B among the excluded articles. It has been placed in the category of selected patients since data were based only on patients who had given their informed, written consent.
With these amendments made according to yourself and the two reviewers, we hope that you will find our paper suitable for publication as a systematic review in the BMC Medicine.

Sincerely Yours

Vidar Ruddox MD