PEER REVIEW HISTORY

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### ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Clinical value of chest pain presentation and prodromes on the assessment of cardiovascular disease; a cohort study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Ayerbe, Luis; Robson, John; Mathur, Rohini; Addo, Juliet; Wragg, Andrew</td>
</tr>
</tbody>
</table>

### VERSION 1 - REVIEW

| REVIEWER | PD Dr. Stefan Bösner, MPH  
Department of General Practice  
University of Marburg  
Germany |
<table>
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<td>GENERAL COMMENTS</td>
<td>thank you for this very interesting manuscript. Please find my few comments below:</td>
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1. Introduction:  
I think that CAD prevalence is overstated; you should rather give a range of the findings in different studies. You should also quote our study (not because it is ours but because it has been so far the biggest prospective study on chest pain in PC (Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sönning AC, et al. Chest pain in primary care: Epidemiology and pre-work-up probabilities. Eur J Gen Pract. 2009;15(3):141-6.)

2. Methods:  
- please give a more detailed account of the logistic regression (e.g. did you use forward or backward selection?)

3. Discussion:  
- Line 42-46: This might apply for the UK; The Marburg Heart Score is part of the official German Chest Pain guideline and used by many GPs in their daily routine.  
It is also part of the current ESC guideline on the management of stable CAD  
("Patients with chest pain are often seen in general practice. Applying a well-validated prediction rule containing the five determinants [viz. age/sex (male ≥ 55 years, female ≥ 65 years); known vascular disease; patient assumes pain is of cardiac origin; pain is worse during exercise and pain is not reproducible by palpation: one point for each determinant] leads to accurate ruling-out of CAD at a specificity of 81% (≤2 points) and a sensitivity of 87% (3–5 points)."
You should discuss this point in a more balanced way.

-Line 51 to 57:
We have described the diagnostic accuracy of these symptoms (dyspnea, dyspepsia) for CAD in a large prospective study (Bösner S, Becker A, Abu Hani M, Keller H, Sönnichsen A, Haasenritter J, et al. Accuracy of symptoms and signs for coronary heart disease in primary care: a diagnostic study with follow up. Br J Gen Pract. 2010;60:420-425.) I can't see a need to repeat this.

A final comment to your categorization for chest pain (specific vs. unspecific). While I think that CP on exertion is a good predictor for CAD, all the other locations are not very discriminative (see also: Bösner S, Bönisch K, Haasenritter J, Schlegel P, Hüllermeier E and Donner-Banzhoff N. Chest pain in primary care: is the localization of pain diagnostically helpful in the critical evaluation of patients? - A cross sectional study. BMC Family Practice 2013, 14:154)

REVIEWER
Rudi Bruyninckx
Rudi Bruyninckx, MD, MSc, PhD
Stafid
Departement Family Medicine
KU Leuven

REVIEW RETURNED
04-Jan-2015

GENERAL COMMENTS
This is a very interesting paper. No physician wants to misdiagnose a patient with CAD. As you write referring patients with low disease will create a lot of financial and personal cost. Not referring patients with high(er) probabilities will destroy the benefits for these patients.

It is important to find the threshold (disease probability) where the expected value of treating (with benefits for the diseased and costs for the non-diseased) is equal to non-treating (with benefits for the non-diseased and cost for the diseased).

I do know Bayes’ Theorem, sensitivity and specificity, positive and negative likelihood-ratios, positive and negative predictive value, thresholds, but I’m not an expert in Hazard Ratios. I suggest adding in the methodology section why you are using the Hazard Ratios. As I understand some literature this method is very useful in hypothesis testing, and that is what you are doing in this paper.

Here my questions and other suggestions.

1) Page 6, 20

- The NICE guidelines recommend that patients should only be referred for further assessment when their likelihood of acute CAD, estimated on clinical grounds, is above 10%’

At my perception, they use the ‘non-angina chest pain’, ‘atypical angina’ and ‘typical angina’ to estimate the disease probability and at a probability of 10% or less to consider another diagnosis.
2) Page 7, 55

‘..all patients aged 30..’

In table 2 is mentioned ‘35+’

3) Page 8, 33; supplement

‘..to define CAD..’

Were there criteria to choose one of the diseases, or was the GP free to select a disease?

I do understand that the list is very extensive for not missing a CAD; this has as consequence that there is a possibility of over-diagnosis.

In the list is also mentioned ‘old myocardial infarction’. This is in contradiction with ‘first ever CAD’ (page 8,21)

3) Page 8, 47

‘..in the 12 months before..”

In table 3 the median time to CAD in months is between 2.6 (specified chest pain) and 6.4 (fatigue),

Is it useful to also use different time slots, like 1, 3 and 6 months? I think that the hazard ratios will be higher.

Can you explain why you are using the 12 moth period. It will create over-diagnosis and more false positives.

Considering 4.842 patients with CAD, 270 with chest pain were misdiagnosed, 495 with prodromi were misdiagnosed, 50 patients are present in both groups (table 2), so in total 715 patients were misdiagnosed. (There are 4.127 (85%) true positives and 715 (14.8) false negatives.)

Those 715 were probably not all ‘false negatives’.

4) Page 8, 50

‘…they were independently associated with CAD..

How do you know they were ‘independently’?
5) Page 9, 44

Those are very interesting numbers for Bayes' Theorem, so I have some questions.

a) How many of the 14,222 patients with reported chest pain had a diagnosis of CAD?

\[
\frac{4,842 \times 100}{14,222} = 34\%
\]

Probably it will be less because not all patients with CAD had chest pain.

I guess around 30% and this is still more than the 20% mentioned on page 6, 20

Problem: no criteria for the diagnosis of CAD and possibility of over-diagnosis?

b) How many of the 70,110 patients with dyspnea, dyspepsia or fatigue had a diagnosis of CAD?

c) How many of the 14,222 patients with chest pain had also dyspnea or/and dyspepsia or/and fatigue en how many of them had a diagnosis of CAD?

If you have those numbers you can calculate the sensitivity, specificity, positive and negative likelihood-ratio of chest pain (3 types), dyspepsia, dyspnea and fatigue for the diagnosis of CAD. In our systematic review (Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome. Br J Gen Pract 2008; 58:105-11) we did not find an important role of signs and symptoms in diagnosing acute myocardial infarction or acute coronary syndrome. Maybe your numbers can give more information.

6) Page 10, 3 and others

‘..chest pain for 70 (25.9%) patients, unspecified for 187 (69.2%) and musculoskeletal for 17 (6.3%)’

Please add 95% CI when using percentages.

7) Page 11, 26

‘Although CAD diagnoses..’

This is an answer on my remark 3.
'Future studies may provide accurate estimation of the risk of CAD in primary care patients with chest pain in association with prodromal symptoms and others CV risk factors'.

See my suggestion 5

9) Page 12, 12

'The association between dyspepsia, dyspnea or fatigue with CAD could also be partially explained by misdiagnosis in some patients e.g.: angina being diagnosed as dyspepsia.'

I do agree with this. Problem is here over-diagnosis, maybe threshold-theory is helpful?

Minor

1) Page 10, 3

25.9 + 69.2 + 10.2 = 101.4 ??

2) Page 10, 8

'...dyspepsia was reported by 232 (46.9%), dyspnea by 235 (47.5%) and fatigue by 54 (10.9 %)..' 

46.9 + 47.5 + 10.9 = 105.3 ??

Maybe this is correct because a patient can have more than 1 prodromi

3) Page 10, 28

9.6 + 70.9 + 24.3 =104.8

4) Page 10, 35

67.9 +27.7 +19.1 = 114.7

Maybe this is correct because a patient can have more than 1 prodromi
5) Page 14, 35
There is missing a ‘h’ in pathways

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports:

Reviewer: 1

Reviewer Name PD Dr. Stefan Bösner, MPH
Institution and Country Department of General Practice
University of Marburg
Germany

Please state any competing interests or state ‘None declared’: Development and publication of the Marburg Heart Score, a validated instrument for ruling out CAD in patients presenting with chest pain in Primary Care.

Dear authors,

Thank you for this very interesting manuscript. Please find my few comments below:

Thanks Dr Bösner for your thorough review. We have modified our manuscript according to each of your suggestions. This has certainly improved the article. Please find our response to each of your comments below:

1. Introduction:

I think that CAD prevalence is overstated; you should rather give a range of the findings in different studies. You should also quote our study (not because it is ours but because it has been so far the biggest prospective study on chest pain in PC (Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sönnichsen AC, et al. Chest pain in primary care: Epidemiology and pre-work-up probabilities. Eur J Gen Pract. 2009;15(3):141-6.)

The prevalence of CAD has been modified. We now report it as a range, citing the studies that observed each result. We have removed one of our previous references. It was an epidemiological study which probably magnified the prevalence of CAD by including participants with chest pain from the population who were not attending GP clinics.

We have included in the manuscript the reference that you suggest.
2. Methods:

Please give a more detailed account of the logistic regression (e.g. did you use forward or backward selection?)

The logistic regression is now presented more in detail.

3. Discussion:

Line 42-46: This might apply for the UK; The Marburg Heart Score is part of the official German Chest Pain guideline and used by many GPs in their daily routine. It is also part of the current ESC guideline on the management of stable CAD

("Patients with chest pain are often seen in general practice. Applying a well-validated prediction rule containing the five determinants [viz. age/sex (male ≥ 55 years, female ≥ 65 years); known vascular disease; patient assumes pain is of cardiac origin; pain is worse during exercise and pain is not reproducible by palpation: one point for each determinant] leads to accurate ruling-out of CAD at a specificity of 81% (≤2 points) and a sensitivity of 87% (3–5 points)." You should discuss this point in a more balanced way.

The discussion has been balanced acknowledging the useful evidence provided by the available scores, including the Marburg (Bösner el al 2010) and the Swiss (Gencer et al 2010) scores derived and validated in primary care.

Line 51 to 57: We have described the diagnostic accuracy of these symptoms (dyspnea, dyspepsia) for CAD in a large prospective study (Bösner S, Becker A, Abu Hani M, Keller H, Sönnichsen A, Haasenritter J, et al. Accuracy of symptoms and signs for coronary heart disease in primary care: a diagnostic study with follow up. Br J Gen Pract. 2010;60:420-425.) I can't see a need to repeat this. This idea considered unnecessary has been deleted from the final version of the text.

A final comment to your categorization for chest pain (specific vs. unspecific). while I think that CP on exertion is a good predictor for CAD, all the other locations are not very discriminative (see also: Bösner S, Bönisch K, Haasenritter J, Schlegel P, Hüllermeier E and Donner-Banzhoff N. Chest pain in primary care: is the localization of pain diagnostically helpful in the critical evaluation of patients? - A cross sectional study. BMC Family Practice 2013, 14:154)

The inclusion of pain location as a criteria for categorisation is now reported as a limitation in the discussion. This limitation is references with the paper that you mention.

Reviewer: 2

Reviewer Name: Rudi Bruyninckx
Institution and Country: KU Leuven

Please state any competing interests or state 'None declared': none declared

This is a very interesting paper. No physician wants to misdiagnose a patient with CAD. As you write referring patients with low disease will create a lot of financial and personal cost. Not referring patients with high(er) probabilities will destroy the benefits for these patients. It is important to find the
threshold (disease probability) where the expected value of treating (with benefits for the diseased and costs for the non-diseased) is equal to non-treating (with benefits for the non-diseased and cost for the diseased).

I do know Bayes’ Theorem, sensitivity and specificity, positive and negative likelihood-ratios, positive and negative predictive value, thresholds, but I am not an expert in Hazard Ratios. I suggest adding in the methodology section why you are using the Hazard Ratios. As I understand some literature this method is very useful in hypothesis testing, and that is what you are doing in this paper.

Dear Dr Bruyninckx

Thanks very much for reviewing our paper. We appreciate that you have found it interesting. We have modified the paper following each of your suggestions. This has certainly improve the paper.

A brief explanation of what thee Hazard ratios are has been included in the methods section.

We respond to the rest of your comments below.

Here my questions and other suggestions.

1) Page 6, 20

‘The NICE guidelines recommend that patients should only be referred for further assessment when their likelihood of acute CAD, estimated on clinical grounds, is above 10%’

At my perception, they use the ‘non-angina chest pain’, ‘atypical angina’ and ‘typical angina’ to estimate the disease probability and at a probability of 10% or less to consider another diagnosis.

We have re-phrased the introduction following your suggestion. The amended manuscript presents the recommendation of the NICE guidelines, more accurately, as you present it.

2) Page 7, 55

‘..all patients aged 30..’

In table 2 is mentioned ‘35+’

Thank you for spotting this. We have corrected the mistake, which was in table 2 The patients are aged 30 or over at entry to the study cohort in 2008 and 35 and over at the end of the study period in 2013.

3) Page 8, 33; supplement

‘..to define CAD..’

Were there criteria to choose one of the diseases, or was the GP free to select a disease? I do understand that the list is very extensive for not missing a CAD; this has as consequence that there is a possibility of over-diagnosis. In the list is also mentioned ‘old myocardial infarction’. This is in contradiction with ‘first ever CAD’ (page 8,21)

In the study we considered CAD if the GP had coded any the terms included in the list. We have modified the methods section to make this more clear.
Old myocardial infarction was not coded so we have removed it from the table.

In the strengths and limitations paragraph, in the discussion, we are acknowledging now that the extensive list used to define CAD may have minimised the number of CADs missing but may have lead to an over reporting of cases.

4) Page 8, 47

‘...in the 12 months before..”

In table 3 the median time to CAD in months is between 2.6 (specified chest pain) and 6.4 (fatigue). Is it useful to also use different time slots, like 1, 3 and 6 months? I think that the hazard ratios will be higher. Can you explain why you are using the 12 month period. It will create over-diagnosis and more false positives.

It was chosen to observe CAD in the year after the start of symptoms because it was considered that both observations within that period of time could be clinically related. We have added this explanation to the methods section of our manuscript. In our preliminary analyses, we explored other periods of time and results were very similar. Since the study is already presenting a substantial number of associations with clinical and epidemiological meaning, we decided to focus only on observations of CAD within 1 year of symptoms. We have modified the manuscript to include your suggestion and we are now acknowledging in the discussion that some of the prodromes and episodes of chest pain observed within a year of CAD may not be clinically related to it. We also suggest that future studies may address the associations of chest pain, and/or prodromes, with CAD in a shorter period of time (i.e. three months)

Considering 4,842 patients with CAD, 270 with chest pain were misdiagnosed, 495 with prodromi were misdiagnosed, 50 patients are present in both groups (table 2), so in total 715 patients were misdiagnosed. (There are 4,127 (85%) true positives and 715 (14.8) false negatives.) Those 715 were probably not all ‘false negatives’.

270 and 495 were the number of patients that went to the GP with chest pain or prodromes in the year before the diagnosis of CAD. We have not used the term misdiagnosis because we actually had no data on the clinical care, including diagnosis and treatment, that these patients had.

We have added a paragraph to the discussion reporting that a large proportion of patients with CAD did not report any kind of symptoms at all to the GP. We suggest that future studies could observe the natural history of CAD in these patients who received no primary care.

5) Page 8, 50

‘...they were independently associated with CAD.. How do you know they were ‘independently’?

We have used the term “independently” to express that the association was significant after adjusting for the confounders mentioned in the methods section. In compliance with your query, we have modified the results section to say this explicitly.

6) Page 9, 44

Those are very interesting numbers for Bayes' Theorem, so I have some questions.
a) How many of the 14,222 patients with reported chest pain had a diagnosis of CAD? $(4,842 \times 100)/14,222 = 34\%$ Probably it will be less because not all patients with CAD had chest pain. I guess around 30\% and this is still more than the 20\% mentioned on page 6, 20. Problem: no criteria for the diagnosis of CAD and possibility of over-diagnosis?

We report the number of patients with CAD who reported chest pain to their GP in the year before 270 (5.6\%) in the second paragraph of the result section. This figure is also presented in table 2. We have added a note to the discussion in which we comment that most patients with CAD did not report chest pain to their GP and the need to investigate these patients who were not seen by a GP in further research. It is also possible that patients with chest pain presented immediately in the hospital and thus the record of chest pain within two years prior to the CAD may not have been present on the GP record.

In accordance with your suggestion, we also discuss the advantages and disadvantages of using an extensive list of codes.

b) How many of the 70,110 patients with dyspnea, dyspepsia or fatigue had a diagnosis of CAD?

495. This figure is reported in table 2.

c) How many of the 14,222 patients with chest pain had also dyspnoea or/and dyspepsia or/and fatigue and how many of them had a diagnosis of CAD? If you have those numbers you can calculate the sensitivity, specificity, positive and negative likelihood-ratio of chest pain (3 types), dyspepsia, dyspnea and fatigue for the diagnosis of CAD. In our systematic review (Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome. Br J Gen Pract 2008; 58:105-11) we did not find an important role of sings and symptoms in diagnosing acute myocardial infarction or acute coronary syndrome. Maybe your numbers can give more information.

The number of patients with prodromes and each type of chest pain is reported in table 3, which also presents the number of them that had CAD.

<table>
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<th>N CAD within 1 year ...</th>
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<td>... ... ... ...</td>
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<tr>
<td>Any chest pain 14,222</td>
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<tr>
<td>Any prodrome + Specified</td>
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<tr>
<td>Any prodrome + Unspecified</td>
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<tr>
<td>Any prodrome + Musculoskeletal</td>
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We are currently working in the development of a score for prediction of CAD in primary care that will use combinations of symptoms. We intend to publish this as a separate paper. This study, as we say in the introduction, is preliminary work exploring the predictive value of chest pain of different tipicality and prodromes to be included in this score.

Acknowledging your comment we have modified the discussion and we report the need for the development of scores that use combinations of symptoms. The reference that you provide has also been included in the list.

7) Page 10, 3 and others
‘chest pain for 70 (25.9%) patients, unspecified for 187 (69.2%) and musculoskeletal for 17 (6.3%)%
Please add 95% CI when using percentages.

Following your comment, we have added 95% CI around the percentages reported in table 1 for our
primary outcomes of CAD after chest pain/prodromes and QRISK>20% after chest pain/prodromes.
Due to the large amount of percentages reported in the text we have not repeated the 95% CI here in
order to keep the text readable.

8) Page 11, 26

‘Although CAD diagnoses..’

This is an answer on my remark 3.

Responding to remark 3, we have modified the methods and the discussion. In the study we
considered CAD if the GP had coded any the terms included in the list. We have modified the
methods section to make this more clear. In the strengths and limitations paragraph, in the
discussion, we are acknowledging now that the extensive list used to define CAD may have
minimised the number of CADs missing but may have lead to an over reporting of cases.

9) Page 11, 52

‘Future studies may provide accurate estimation of the risk of CAD in primary care patients with chest
pain in association with prodromal symptoms and others CV risk factors’.

See my suggestion 5

We are actually working in a score that will combine symptoms to predict CAD. As presented in the
introduction, this is preliminary work to explore the use of typicality and prodromes.

10) Page 12, 12

‘The association between dyspepsia, dyspnea or fatigue with CAD could also be partially explained by
misdiagnosis in some patients e.g.: angina being diagnosed as dyspepsia.’

I do agree with this. Problem is here over-diagnosis, maybe threshold-theory is helpful?

Following your comment we have added to the discussion a paragraph that addresses the possibility
of over diagnosis.

Minor

1) Page 10, 3

25.9 + 69.2 + 10.2 = 101.4 ??

This is correct as a patient may have more than 1 chest pain diagnosis in the year prior. The text has
been changed to reflect this more clearly.

2) Page 10, 8
‘..dyspepsia was reported by 232 (46.9%), dyspnea by 235 (47.5%) and fatigue by 54 (10.9 %).

46.9 + 47.5 + 10.9 = 105.3 ??
This is correct because a patient can have more than 1 prodrome prior to their CAD event

3) Page 10, 28

9.6 + 70.9 + 24.3 = 104.8
This is correct as a patient may have more than 1 chest pain diagnosis before QRISK >20%. The text has been changed to reflect this more clearly.

4) Page 10, 35

67.9 +27.7 + 19.1 = 114.7
This is correct because a patient can have more than 1 prodrome

The numbers for chest pain and prodromes are correct as patients can present with more than one prodrome or chest pain prior to the CAD event. For the purposes of calculating the risk of CAD after experiencing multiple prodromes or chest pain, the date of the prodrome or chest pain closest to the CAD event was used.

5) Page 14, 35

There is missing a ‘h’ in pathways
Thanks for spotting this. We have amended the mistake

VERSION 2 – REVIEW

| REVIEWER | PD Dr. Stefan Bösner  
Department of General Practice  
University of Marburg  
Germany |
<table>
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<td>20-Jan-2015</td>
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| GENERAL COMMENTS | The authors have incorporated all suggested changes |

| REVIEWER | Rudi Bruyninckx  
Department of Public Health and Primary Care KU Leuven  
Kapucijnenvoer 33, Blok J, PB 7001, 3000 Leuven, Belgium |
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<td>REVIEW RETURNED</td>
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| GENERAL COMMENTS | It was a pleasure to review this article. Congratulations. |
Clinical value of chest pain presentation and prodromes on the assessment of cardiovascular disease: a cohort study

John Robson, Luis Ayerbe, Rohini Mathur, Juliet Addo and Andrew Wragg

BMJ Open 2015 5:
doi: 10.1136/bmjopen-2014-007251

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These include:

Supplementary Material
Supplementary material can be found at:
http://bmjopen.bmj.com/content/suppl/2015/04/15/bmjopen-2014-007251.DC1

References
This article cites 29 articles, 9 of which you can access for free at:
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