PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic accuracy of Copeptin sensitivity and specificity in patients with suspected non–ST-elevation myocardial infarction with troponin I below the 99th percentile at presentation.
AUTHORS	DUCHENNE, Jonathan; Mestres, Stéphanie; Dublanchet, Nicolas; Combaret, Nicolas; Marceau, Geoffroy; Caumon, Laurent; Dutoit, Laurent; Ughetto, Sylvie; Motreff, Pascal; Sapin, Vincent; SCHMIDT, Jeannot

VERSION 1 - REVIEW

REVIEWER	Pere Llorens Emergency Department Hospital General Universitario de Alicante Alicante. Spain.
REVIEW RETURNED	02-Jan-2014

| GENERAL COMMENTS | The Editorial Committee :

To an inquiry about publishing in BMJ -open work " Diagnostic accuracy of sensitivity and specificity Copeptin in patients with Suspected non -ST- elevation myocardial infarction with troponin I below the 99th percentile at presentation "

This is a prospective, cohort study , multicenter where the main objective of this study is evaluate- copeptin whether the addition of troponin measurement to the first determination Allows non -ST- elevation acute myocardial infarction (NSTEMI) to be ruled out in patients consulting the emergency department (ED) for non - traumatic chest pain suggestive of acute coronary syndrome whose first electrocardiogram and troponin determination are non - diagnostic .

The authors have developed an interesting study where they add more information about the usefulness of copeptin in NSTMI in the ED . Are knowledgeable of the subject matter and have used current and recent literature.

Considerations :

Abstract:

In the results section and in the rest of the text the authors use both the concept of " NSTEMI " as " AMI " , should be unified and a designation used only when referring to patients with non -ST- elevation myocardial infarction , and no use the concept "AMI" , leading to compression errors .

Methods : |

Population : Inclusion criteria should explain more extensively and adding electrocardiographic criteria were used.

Outcomes :
It is necessary for the definition and criteria used to place the diagnosis of NSTEMI , unstable angina pectoris , cardiac and coronary artery disease but non are added , as this description is the basis of the study and has not been sufficiently developed

Limitations of the study

Post after quoting reference " Reichlin "

Discussion:

We suggest removing the first paragraph as the authors explain again the purpose of the study and provides no information on the discussion.

Most authors define as a biomarker copeptin to rule out MI and not other types of acute coronary syndrome . It is Known patients with unstable angina that have copeptin concentrations lower than those with NSTEMI or even have Which are similar to levels in patients Those with other non ischemic causes of chest pain . This important point would be added to the limitations in paragraph discussion

tables:

Table 1:

Add in the first column :

In patients (n (%))

In Age : years [mean (SD)] and set the example : 59 (16) by removing " ± " . (remove the decimal age)

Body Mass Index (kg/m2) , [mean (SD)]

etc.

REVIEWER	Prof P O Collinson Clinical Blood Sciences St George's Hospital London UK
REVIEW RETURNED	07-Jan-2014

GENERAL COMMENTS	The authors have undertaken an assessment of the diagnostic efficiency of admission measurement of co-pectin in patients with a non-diagnostic ECG and a cardiac troponin I below the 99th percentile on presentation with chest pain. The authors conclude that the diagnostic efficiency of co-pectin measurement is insufficient for use as a rule out test.

The principal problem with this study is, on the authors own admission, the relatively small numbers though they consider that were diagnostic efficiency adequate it would have performed better than the poor efficiency that they found in their study.

The authors need to address the following points.

1. In the methods section the authors should state the criteria that they used for family history of coronary artery disease, hypertension, hyperlipidaemia and diabetes mellitus (mentioned in table 1).

2. The authors should use SI units throughout the manuscript. The analytical imprecision of the myoglobin method should be added.

3. For the diagnosis of myocardial infarction the authors do not state which troponin value was used. Presumably this was peak value of the serial samples.

4. The authors cite the most recent publications on co-peptin but do not put their work in context with it. The discussion should critically appraise their findings in respect of the initial previous published reports.

Finally, the manuscript contains a few idiosyncrasies such as the use of the term the term natraemia and misspelling of creatinine.

REVIEWER	Kai M Eggers
	Uppsala University, Sweden
REVIEW RETURNED	08-Jan-2014

GENERAL COMMENTS	I have read the paper from Duchenne and colleagues with interest. The authors investigated the diagnostic properties of serially measured copeptin levels in a small sample of chest pain patients who had non-elevated high-sensitivity troponin I (cTnI) upon admission to the emergency department. Interestingly, copeptin was mostly below the diagnostic cut-off despite a rather short time from symptom onset among MI patients (mean 2.5 hrs), and did not increase over time.
	The authors address a timely topic, i.e. the facilitation of early ruling-out of MI in the context of contemporary biomarkers of myocardial necrosis. The main limitation, as acknowledged by the authors, is the small sample size and the limited number of patients with acute coronary syndrome (NSTEMI: n=8; unstable angina: n=4). For this reason, the analyses remained mainly descriptive in nature. However, I have some additional questions and remarks that should be addressed:
	Major comments:
	1. How was unstable angina defined ?
	2. The sample size calculation is not clear. Was a statistical power of 80% (page 3; last para) or of 95% (page 6; statistical analysis) intended ?
	3. Page 3; last para: The authors speculate on the diagnostic performance of copeptin if their study had been adequately powered. I recommend to skip this issue here and elsewhere in the manuscript (page 9) as it is purely hypothetic.
	4. Page 8; 2nd para: The results on cTnI do not really add much information. Per protocol, all patients had to be cTnI-negative upon admission and not surprisingly, all MI-patients had elevated levels. Also, the analytical imprecision of the applied assay at low cTnI levels is a confounder. Nevertheless, Figure 2 is useful to illustrate

	the different kinetics between cTnI and copeptin.
	5. What was the rationale to assess myoglobin and creatine-kinase ? These are historic biomarkers and should no longer be used.
	6. The patients were followed-up after 90 days but further information on the investigated endpoints and the prognostic implications of the assessed biomarkers are missing.
	7. The paper would benefit if it was cross-checked for style and grammar.
	Minor comments:
	1. Suggest to report p-values with two digits unless p<0.01.
	2. Page 4; 1st para: copeptin is part of uncleaved pro-arginin-vasopressin, not a surrogate marker. Suggest to re-formulate this sentence and to select more specific references on the physiology of copeptin.
	3. Figures 4 and 5 appear in the wrong order.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name : Pere Llorens
Abstract:
In the results section and in the rest of the text the authors use both the concept of " NSTEMI " as " AMI " , should be unified and a designation used only when referring to patients with non -ST-elevation myocardial infarction , and no use the concept "AMI" , leading to compression errors .

The manuscript was standardized with the term NSTEMI.

Methods :
Population : Inclusion criteria should explain more extensively and adding electrocardiographic criteria were used.

We modified the manuscript and added:
- The pain criteria used for inclusion
- The criteria used to define an ST-segment elevation
- The rationale for non-inclusion criteria

Outcomes :
It is necessary for the definition and criteria used to place the diagnosis of NSTEMI , unstable angina pectoris , cardiac and coronary artery disease but non are added , as this description is the basis of the study and has not been sufficiently developed

The definition of different diagnostic categories were developed.

Limitations of the study
Post after quoting reference " Reichlin "

Corrections made.

Discussion:
We suggest removing the first paragraph as the authors explain again the purpose of the study and provides no information on the discussion.
Most authors define as a biomarker copeptin to rule out MI and not other types of acute coronary syndrome . It is Known patients with unstable angina that have copeptin concentrations lower than those with NSTEMI or even have Which are similar to levels in patients Those with other non

ischemic causes of chest pain . This important point would be added to the limitations in paragraph discussion

We removed a part of the first paragraph of discussion, redundant with the introduction.
We added, in the discussion section, a paragraph putting into perspective the fact that our study population, the patients had infarct size probably small (hs-cTnI below the 99th percentile at admission), could be comparable to patients with unstable angina for which levels of copeptin does not increase.

tables:

Table 1:
Add in the first column :

In patients (n (%))
In Age : years [mean (SD)] and set the example : 59 (16) by removing " ± " . (remove the decimal age)
Body Mass Index (kg/m2) , [mean (SD)]
etc.

Corrections made.

Reviewer Name : Prof P O Collinson

1. In the methods section the authors should state the criteria that they used for family history of coronary artery disease, hypertension, hyperlipidaemia and diabetes mellitus (mentioned in table 1).

The collection mode of these criterias were detailed in method section. Family history were also defined.

2. The authors should use SI units throughout the manuscript. The analytical imprecision of the myoglobin method should be added.

We expressed results for myoglobin in µg/L to conforming to SI.
Coefficient of variation intra- and inter-essay at concentrations of 110 ng/mL were added.

3. For the diagnosis of myocardial infarction the authors do not state which troponin value was used. Presumably this was peak value of the serial samples.

We clarified the method with which we have interpreted the values of troponin for the diagnosis of NSTEMI in the method section.

4. The authors cite the most recent publications on co-peptin but do not put their work in context with it. The discussion should critically appraise their findings in respect of the initial previous published reports.

We added in the discussion section a paragraph in which we study trials evaluating copeptin with hs-cTn, and with which we compare our results. Equally, we added the last two studies published after the initial submission of the manuscript.

Finally, the manuscript contains a few idiosyncrasies such as the use of the term the term natraemia and misspelling of creatinine.

Corrections made.

Reviewer Name : Kai M Eggers

Major comments:
1. How was unstable angina defined ?

The definition of different diagnostic categories were developed in the methods section.
The defining criterias unstable angina were the same as those defining the NSTEMI, without elevation of troponin. (NSTEMI defined by a rise and/or fall of hs-cTnI with at least one value above the 99th percentile and with the following : imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or   identification of an intracoronary thrombus by angiography.)

2. The sample size calculation is not clear. Was a statistical power of 80% (page 3; last para) or of 95% (page 6; statistical analysis) intended ?

Our statistician confirms that the power used to calculate the number of subjects is 95%. This error occurred after the article writing, during the preparation of the summary section "strengths and limitations of this study".

3. Page 3; last para: The authors speculate on the diagnostic performance of copeptin if their study had been adequately powered. I recommend to skip this issue here and elsewhere in the manuscript (page 9) as it is purely hypothetic.

Indeed, this speculation is not within a scientific approach. We removed these two paragraphs.

4. Page 8; 2nd para: The results on cTnI do not really add much information. Per protocol, all patients had to be cTnI-negative upon admission and not surprisingly, all MI-patients had elevated levels. Also, the analytical imprecision of the applied assay at low cTnI levels is a confounder. Nevertheless, Figure 2 is useful to illustrate the different kinetics between cTnI and copeptin.

The analytical accuracy of this hs-cTnI do not allowed to compare troponin values lower than 0.040 mg / L (CV <10%). We removed these description.

5. What was the rationale to assess myoglobin and creatine-kinase ? These are historic biomarkers and should no longer be used.

Myoglobin has long been considered and sometimes used as an early marker of myocardial infarction. Copeptin is sometimes compared to myoglobin and described as a "super-myoglobin" for the diagnosis of MI because of its kinetics. We wanted to compare copeptin with this historical marker, although it is no longer recommended.
Dosage of CK is recommanded if troponin is not available. Furthermore, in some local centers, the CK assay in addition to troponin is always performed for the diagnosis of MI. This helps to show by a local study the uselessness of this diagnostic practice.

6. The patients were followed-up after 90 days but further information on the investigated endpoints and the prognostic implications of the assessed biomarkers are missing.

We clarified the origin of the data collected at the end of follow-up in the method section. The proportion of patients who had echocardiography, cardiac exercise test, and coronary angiography is indicated in Table 1.

The prognosis implication of biomarkers studied was not in the objectives of the study. however, we noted in the discussion that the only NSTEMI patient who had high copeptin level died.

7. The paper would benefit if it was cross-checked for style and grammar.

Corrections made.

Minor comments:
1. Suggest to report p-values with two digits unless $p < 0.01$.

Corrections made.

2. Page 4; 1st para: copeptin is part of uncleaved pro-arginin-vasopressin, not a surrogate marker. Suggest to re-formulate this sentence and to select more specific references on the physiology of copeptin.

Corrections made and a short section on the physiology of copeptin was added with references.

3. Figures 4 and 5 appear in the wrong order.

Corrections made.

VERSION 2 – REVIEW

REVIEWER	Pere Llorens Emergency Department Hospital General de Alicante Alicante. Spain
REVIEW RETURNED	25-Feb-2014

GENERAL COMMENTS	The authors have modified the article correctly and have added all the recommended suggestions

REVIEWER	Professor Paul Collinson St George's Hospital, London
REVIEW RETURNED	17-Feb-2014

- The reviewer completed the checklist but made no further comments.