Author's response to reviews

Title: Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study

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Author's response to reviews: see over
Dear Editor

Please find enclosed our revised manuscript: “Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study.” We thank the reviewers for their comments. Below you will find our point-to-point answers to the comments made by the reviewers and the Editor with references to where the corresponding changes have been made in the manuscript.

We thank the Editor for giving us the opportunity to make this revision. We believe the revised paper is improved compared to the original version and hope you will find it suitable for publication.

Sincerely yours,
Reviewer's report

Title: Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study

Version: 1 Date: 20 November 2011
Reviewer: Konstantinos Kostikas

Reviewer's comment:
The fact that the authors have evaluated only the determinants of hs-cTnT without evaluating its prognostic value reduces the clinical impact of a prospective cohort study. One would expect from such a study design to evaluate clinically important outcomes (e.g. outcomes of AECOPD, survival, future AECOPD etc.)

Author's reply:
We do agree with the reviewer that a prospective cohort study is well suited for evaluation of outcomes such as survival and readmissions. In a previous publication (reference 13 in the revised article), we did indeed find a strong association between the level of hs-cTnT and mortality. Given the concept of “the frequent exacerbation phenotype”, it would also be interesting to investigate whether there is a relationship between hs-cTnT and exacerbation frequency, with the hypothesis that the frequent exacerbators are in fact patients with poorly appreciated heart disease. This remains to be investigated, but may be the topic of future publications.

Reviewer's comment:
The longitudinal design of the study includes patients with one and several AECOPD in the same analysis. Patients with several admissions for AECOPD represent a significant bias in such an analysis. The authors have attempted to overcome this by using LMMs, but the bias is still present, since we are talking about multiple inclusions of the same patients. The evaluation of repeatability and reproducibility of hs-cTnT on two consecutive AECOPD would be important information to include in the analysis.

Author's reply:
We appreciate this comment from the reviewer. We admit that the analytical approach to these data is not straightforward. However, we do not quite understand how the reviewer interpret the concept “bias” in these settings. The strength of the method we chose (LMM – contrary to alternative methods such as GEE) is that it allows data to be highly unbalanced, i.e. different number of follow-ups as well as different time intervals between the study subjects. (See Fitzmaurice GM, Laird NM and Ware JH. Applied Longitudinal Analysis, New York. John Wiley 2004.) Actually, this method enables two (or more) consecutive AECOPDs to be compared, thereby analysing the association between two (or more) variables like cTnT and hypoxemia within each individual under different conditions. On this matter, we have added the following to the Discussion section:

Page 11, paragraph 2, lines 4-6: Moreover, by using an appropriate covariance structure, the model allows us to have unbalanced data with different number of observations per patient and different timing of these.
Reviewer's comment:
Disease severity based on the spirometry data presented in the Methods section is unacceptable. The authors state that "Spirometry during stable phase, preferably post bronchodilatation measurements taken prior to inclusion, was recorded when available." Post-bronchodilator spirometry data would be required and disease severity according to FEV1 might be an important determinant of hs-cTnT that is not properly evaluated in this study.

Author's reply:
We thank the reviewer for this comment. We do certainly agree that lung function is central in any paper addressing comorbidities in COPD patients. We did only record spirometry data from stable phase as lung function during the recovery from an exacerbation is lower and poorly suited for comparison with measurements taken in stable phase. Regrettably, stable phase recordings were only available in 88 patients, even after thorough search in the hospital records and on collaborating hospitals.

An important question raised by the reviewer is whether missing spirometries or measurements without bronchodilatation introduce bias in our analyses. Of the 88 spirometries recorded, 80 (91%) were post bronchodilatation measurements from the outpatient clinic. In the remaining eight measurements, collected from primary physicians and hospital records, this was either unclear or not the case.

In the 88 patients with spirometry available, we did analyse cross-sectional associations between hs-cTnT and lung function and found no statistically significant association. In Table 1 in our previous publication based on this cohort (reference 13 in the revised paper) we found p-values of 0.77 and 0.69 for Chi-square analyses of the association between hs-cTnT (categorised in three) and FEV1/FVC-ratio and FEV1, respectively. In the present study, we analysed the association between hs-cTnT (as a continuous variable) and FEV1/FVC-ratio in the lower quartile using Student’s t-test. The p-value was 0.945. We also performed a linear regression analysis between FEV1/FVC and hs-cTnT. The p-value was 0.868. Using the 80 post bronchodilatation measurements only, the corresponding t-test and linear regression p-values were 0.890 and 0.803, respectively.

In the case of a statistically significant association between lung function and hs-cTnT, inclusion of lung function in the analyses and restriction of the analyses to the 88 patients with lung function recorded or to the 80 patients with post bronchodilatation measurements, would have been appropriate. As this was not the case, all 99 patients were included in the analysis.

A related issue is whether the distribution of hs-cTnT was different among the patients who had spirometry available and those who had not. Comparing the natural logarithm of hs-cTnT among patients with and without spirometry available showed no significant difference: Geometric means of 26.4 and 20.9 ng/L, respectively, p-value 0.438.

As we do agree that any potential association with lung function is important to elucidate, we have made the following additions in the manuscript:

In the methods section:
Page 5, paragraph 2, lines 1-4: Spirometry during stable phase was recorded when available. When several measurements were done, post bronchodilatation measurements prior to inclusion were preferred. Body mass index (BMI) was calculated from weight and height as recorded on the spirometry report or from the hospital records when spirometry was missing.

In the results section:
Page 8 paragraph 2, first two lines: Spirometry was available in 88 patients. 80 of these (91%) were post bronchodilatation measurements.

Page 8, paragraph 2, last seven lines: Moreover, we did not find any association between hs-cTnT and lung function. The patients with FEV\textsubscript{1}/FVC in the lower quartile (<0.34 %) had a geometric mean of hs-cTnT = 26.1 ng/L compared to 26.6 ng/L among patients with FEV1/FVC in the upper three quartiles (p= 0.945). When restricting the analysis to the 80 patients with post bronchodilatation measurements, the p-value was 0.890. There was no statistically significant difference in hs-cTnT level among patients who had spirometry recorded and those who had not (geometric mean of 26.4 ng/L and 20.9 ng/L, respectively, p=0.438).

**Reviewer's comment:**
A lot of information presented in the Results section would rather be presented in the Methods section (e.g. hs-cTnT values assigned to patients with levels below the detection limit, outliers, methods for GFR etc.)

**Author's reply**
We thank the reviewer for this pertinent comment. To improve the manuscript, we have moved the following to the Methods section:

Page 6, lines 2-5: Samples with hs-cTnT below the limit of detection (i.e. 3.0 ng/L), were assigned a value of 3.0. Outliers were identified by visual inspection of the data points. Individual assessment of outliers determined whether they were to be excluded from further analyses.

Page 7, paragraph 2, last line: Gender was kept in the model by convention.

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**Reviewer's report**

**Title:** Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study

**Version:** 1  **Date:** 29 November 2011

**Reviewer:** Jadwiga Wedzicha

**Reviewer's comment:**
The authors have divided up the cross sectional and longitudinal data and they must also separate out patients with repeat events that has been partially done. It is important that analysis of biomarker prediction is performed on one event only as otherwise there will be bias.

**Author's reply:**
We do understand the reviewer’s concerns regarding bias when analysing repeat observations on the same subject. Respectfully, we do not share the reviewer’s view that we introduce bias when doing so in this case. Though rarely used, the linear mixed model is well described in the literature. (See Fitzmaurice GM, Laird NM and
Among the strengths of the model is that it enables researchers to investigate longitudinal data on individuals. By choosing a covariance structure (spatial exponential in this case) that fits the temporal distribution of the data, we believe that we can validly analyse these unbalanced data.

**Reviewer's comment:**
The references need a bit of work and the authors have left out Donaldson et al in Chest 2010 that describes the relation of MI and COPD exacerbations. there is also some literature around fibrinogen a a risk factor at exacerbations that needs to be included.

**Author's reply:**
We thank the reviewer for pointing this out and do appreciate the possibility to add relevant references. To improve the article, we have added the Donaldson-reference to the Introduction:

Page 3, lines 4-7: ...and it is proposed that “systemic spill-over” from lung inflammation in COPD may explain the increased cardiovascular risk among these patients, both in general and particulary post exacerbation.

References to papers on fibrinogen have been made in the Discussion section:

Page 12, paragraph 2, lines 9-13: Other markers of inflammation than leucocytes, fibrinogen in particular, have been shown to be associated with COPD, its severity and exacerbation frequency.[22-27] Fibrinogen was not measured in this study, but one might speculate whether this inflammatory marker might be more closely associated with cTnT, as it may be a risk factor for the development of CVD.

**Editorial comment:**
Neither reviewer felt able to assess the statistical content of your manuscript. Please note that, on submission of your revised manuscript, we will approach an additional reviewer to assess this aspect of your study.

**Author's reply:**
We appreciate and welcome the review of an additional reviewer with special expertise on statistics. We do realize that the statistical method used is beyond what is considered the standard statistical repertoire of clinical researchers. Still, we have chosen to apply the linear mixed model. It enables us to investigate both intra- and interindividual associations, bringing new insight to the research field, by using the patients as their own contols.

Above, we have addressed the concerns raised by the reviewers regarding bias, and believe that you will be convinced that the model is applicable to our data.

**Editorial comment:**
Informed consent must be documented in your manuscript. Manuscripts may be rejected if the editorial office considers that the research has not been carried out
within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Author’s reply:
We thank the editor for pointing this out. We can assure the editor that all patients provided written informed consent. In the revised manuscript, the following addition is made in the Methods section:

Page 5, last line: All included patients provided written informed consent to the participation in the study.