Author’s response to reviews

Title: Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial

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Version: 3 Date: 30 November 2010

Author’s response to reviews: see over
Zurich, 30 November 2010

MS: 6806930873847505 - Clinical benefit of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial.

Dear Editors,

Thank you for accepting the delaying of our revision. Please find in the next pages our point-by-point response to your questions and to the reviewer's commentaries.

Sincerely

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Yuki Tomonaga
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Thomas D. Szucs
Prof. Dr. med.
Journal comments:

In addition to the comments raised by the reviewers, please address the following editorial points:

1. Trial Registration Number: We notice that you are reporting a controlled clinical trial but have not cited a trial registration number. This must be attained before we can complete the peer review of your manuscript.

BioMed Central has always supported initiatives to improve the performance and reporting of clinical trials, part of which includes prospective registering and numbering of trials. BioMed Central requests a trial registration number for manuscripts reporting work that falls within the International Committee of Medical Journal Editors (ICMJE)’s definition of a clinical trial: any research study that prospectively assigns human subjects to one or more health related interventions to evaluate the effects on health outcomes.

We would like you to confirm that your clinical trial is in a publicly accessible registry. The trial registration number should be included as the last line of the abstract of the manuscript. The last section of the abstract should be Trial Registration: listing the trial registry and the unique identifying number, e.g. Trial registration: Current Controlled Trials ISRCTN73824458. Please note that there should be no space between the letters and numbers of the trial registration number.

Please note that we accept registration numbers issued by registries that meet all of the ICMJE criteria (http://www.icmje.org/publishing_10register.html). Registries which meet the requirements of the ICMJE include WHO Primary Registries (http://www.who.int/ictrp/network/primary/en/index.html).

If you have applied to register your trial but are experiencing delays please provide us with the details of your registration.

Reply: Concerning the trial registration, we unfortunately cannot provide a registration number. Actually, as the study organisation started in 2006, we didn’t consider a trial registration. Several reasons accounted for this decision: first, in 2006, it was not yet a consuetude to register such kind of trial in Switzerland. Second, since the selected biomarkers were already known and the diagnostic devices were already commercialised, we and the ethic committee didn’t consider it mandatory to register the study. Finally, since the study was conducted only in the Canton of Zurich, all documents were written in German, which may have been a problem for a trial registration (we had no time or resources to translate all documents in English).

Concerning the public accessibility, the study documents (protocol, patient information, questionnaire, etc.) should be available at the ethic committee of the Canton of Zurich. (Please note that in 2006 the study submission system was not yet electronic... therefore, it would be simpler and faster to contact me or Prof. Thomas Szucs in order to receive an electronic version).
Point-by-point response
Reviewer: Caroline Laurence

Minor Essential Revisions

The methods section does require further refinement. While the authors stated that the omissions in the methods section were reported elsewhere in the paper (e.g., discussion or introduction), these should all be included in the methods section so that readers can easily determine the approach taken without having to review the whole paper to determine what was done. For example, the IQC and EQA should appear in methods, not discussion.

Reply: IQC and EQA appear now in the methods (Technical information).

Working diagnosis versus confirmed diagnosis
I am still not clear what the difference between these two diagnoses are apart from a time period of 3 weeks.

Reply: The difference is that after 3 weeks it should be clear if the working diagnoses of ACS/HF/TE (i.e., the preliminary diagnosis or diagnostic hypothesis) were correct or not (in particular the false positive diagnoses should have been identified). Therefore we considered the follow-up diagnosis as confirmed (=correct) diagnosis. As already explained this is a limitation of the study: “In principle, the confirmed diagnoses should have been performed by independent blinded assessors, but this was not feasible. For practical and data protection reasons, they were made by the same physician who was primarily consulted by the patient. We are aware of the potential for bias, e.g., due to possible underreporting of incorrect baseline diagnoses leading to a false high rate of correct baseline diagnoses or a false low difference between study arms. On the other hand, for patients referred for further diagnostic work-up (including all patients at potentially high cardiovascular risk), GPs received a written report on the second-stage assessment as well as information on further clinical management, which substantially reduced the risk of bias.”
Point-by-point response
Reviewer: Andrew R Willan

Major Essential Revisions
1. The statement in the abstract, “The 218 POCT patients and 151 conventional diagnosis controls were similar in characteristics, symptoms and pre-existing diagnoses” contradicts the statement on page 6: “The groups statistically differed in rates of acute chest and calf pain.” This needs to be rectified.

Reply: We corrected in the abstract: “The 218 POCT patients and 151 conventional diagnosis controls were mostly similar in characteristics, symptoms and pre-existing diagnoses”

2. The justification for the non-inclusion criteria, except refusal of consent, should be given.

Reply: Justifications were added.
“Non-inclusion criteria were refusal of consent, presentation >5 days after symptom onset, recent anticoagulant treatment, severe renal dysfunction and cancer therapy. Rationales for the exclusion criteria were the normalisation of the cTnT level five days after ACS, the fact that cTnT may be increased even in the absence of clinically suspected acute myocardial ischemia in patients with renal insufficiency, and the unpredictable effect of anticoagulant treatment and cancer therapy on the biomarkers’ concentration.”

3. What measures were in place to insure that all potentially eligible patients were approached.

Reply: As in almost all studies conducted in a primary care setting it was impossible to insure the recruitment of all potentially eligible patients. In fact, it ultimately depended on the practitioner if a patient was included or not. We personally visited all practice 1-2 times and we telephonically contacted them to remind them to recruit all eligible patients.

4. The statements “Intergroup comparisons were performed using the chi-square test for categorical data and Student’s t-test for independent groups for continuous data. A p value <0.05 was deemed statistically significant; p values were adjusted for the effect of clustering utilising a generalised estimating equations approach.” are contradictory. If generalized estimating equations were used to adjust for the clustering then clearly chi-squared and t-test were not used to compare groups. This needs to be clarified.

Reply: We have corrected the statement: "Intergroup comparisons of categorical data were performed using univariate logistic regression; standard errors and p values were adjusted for the effect of clustering utilising a generalised estimating equations approach."
5. The statement on page 7, “(due to two false-negative ACS in the POCT group in patients given a working diagnosis of stable angina)” should be removed. The comparison of the sensitivities depends on all the data from both groups, and it is very misleading to state that the comparison hinged on the observations on two patients. The statement should be removed.

Reply: Agree. We removed the statement.

6. I don’t understand the statement “A second limitation could be the selection of the patients: as shown in figure 1, the diagnostic frequencies by the working diagnoses in the two groups were significantly different.” The POCT group had more diagnostic information (i.e. the biomarkers), so surely you wouldn’t expect the working diagnoses in the two groups to be the same. I thought that was the whole point of the trial. This limitation should be removed.

Reply: In fact Prof. Willan is right. This is not really a limitation. It is just a confirmation that the two patient populations were more similar than suspected. We removed the statement.

7. The sampling error as described as “A third limitation could be the physician randomisation. Although the mean year of medical qualification was similar in both physician groups, as were the patient characteristics, it cannot be excluded that the study results were affected by residual confounding or chance effects.” Is not a specific issue for this study, but is an issue for all empirical research. The additional uncertainty due to randomizing practices, rather than patients, is reflected in the p-values since the authors accounted for the clustering in the analysis. I recommend removing this as “limitation”.

Reply: Agree. Statement was removed.

PS: Please note that Matthias Schwenkglenks recently changed affiliation.