Author's response to reviews

Title: Long-term outcome of infective endocarditis: a study on patients surviving over one year after the initial episode treated in a Finnish teaching hospital during 25 years

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Author's response to reviews: see over
Dear Editor

Thank you for your positive letter regarding our manuscript: MS: 5666109001596981 entitled “Long-term outcome of infective endocarditis: a study on patients treated in a Finnish teaching hospital during 25 years” by Maija Heiro, Hans Helenius, Saija Hurme, Timo Savunen, Kaj Metsarinne, Erik Engblom, Jukka Nikoskelainen and myself. We were pleased to receive a request of a revised version of the manuscript. We found the criticism and comments presented by the Reviewers constructive, and feel that they have greatly helped us to improve the manuscript. The manuscript has now been revised according to these suggestions. We include here a list providing point-by-point responses to all of the Reviewers’ comments and indicating the changes made according to their suggestions.

Following the requirement of Reviewer 1, we have changed the study population in the majority of the analyses to include only those patients who survived more than one year. Therefore, we propose a new title for the revised manuscript to read as follows: “Long-term outcome of infective endocarditis: a study on patients surviving over one year after the initial episode treated in a Finnish teaching hospital during 25 years.”

Following the suggestion of Reviewer 3, we have analysed separately the 1-year survivors for only the first episode of infective endocarditis regarding the overall and cardiac mortality. Also these results have been presented in the text.

We hope that after these revisions and clarifications, you will find this paper satisfactory and suitable to be published in your Journal. Finally, we would like to thank you and the Reviewers for your time, consideration and valuable criticism.

Yours sincerely,

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Reviewer 1 (Ana Revilla)

Major Compulsory Revisions

Comment 1.
The Reviewer focuses severe criticism on our study arrangement, i.e. when the long-term (> one year) outcome of the patients was evaluated, not only those patients who survived over one year, but also those who died during one year were included in the statistical analyses. The Reviewer rightfully claims that such analyses are influenced by patients who have events within one year. Further, in the second part of the study involving the in-hospital survivors as a separate study group, also patients surviving the acute episode of infective endocarditis (IE) but dying within one year were included, similarly influencing the statistical analyses. Moreover, the Reviewer points out that the most important analyses, i.e. regarding the factors predicting the outcome among patients surviving more than one year is lacking.

Response:
We feel that these points of the Reviewer are completely justified. Therefore, following his/her suggestion, we have changed the study population to include in the majority of the analyses only those patients who survived more than one year.

In the revised manuscript, only the one-year survivors have been included in the analyses focusing on the association between various clinical characteristics during the initial episode of IE and the overall mortality, cardiac mortality, and late valve surgery. Despite this major change in the study composition, the main findings changed only little. The major differences between the results of the original version and the revised version of the manuscript are that when only the one-year survivors were analysed, 1) the presence of a neurological complication during the initial episode of IE was not significantly associated with increased long-term overall mortality and that 2) the long-term cardiac mortality was not significantly associated with neurological complications and collagen disease.

Comment 2.
The Reviewer points out that in our previous study (Heiro et al. BMC Infect Dis 2007, 7:7), heart failure was found to be the most important predicting factor of mortality during the initial hospitalisation and, even thereafter, up to one year of the follow-up. The Reviewer criticises that when we in this study aim at analysing whether heart failure during the initial episode of IE still after one year influences the prognosis of the patients, also those dying during one year were included in the statistical analyses. In contrast, the Reviewer’s feels that only patients who survived over one year should have been included in the analyses. The basis for this requirement is that one-year survivors are probably not so influenced by the characteristics of the acute episode.
Response:
We can well understand also this point of the Reviewer and agree with his/her reasoning. A much more correct picture can be obtained, if only the one-year survivors are included. Consequently, only these patients were included in the statistical analyses of the revised manuscript (see above, Response to Comment 1). The result was that even in this patient population, heart failure within 3 months was significantly associated with increased long-term overall mortality and increased long-term cardiac mortality.

Minor essential revisions

Comment 1.
Consistent with the contents of the Discussion section of the present manuscript, the Reviewer comments on that the influence of cardiac surgery on the prognosis of the patients with IE is still a matter of debate and controversy. Although some papers point out that surgery improves the prognosis of these patients, this is not a constant finding.

The results of the present paper suggest that the patients who underwent surgery during the initial hospitalisation had a better prognosis than those who did not. The Reviewer suspects, however, that these results may not be quite accurate since there may have been patients who had indication for surgery but were for some reason rejected for surgery. Therefore, he/she suggests that to avoid this bias, two patient groups should be compared: patients operated on versus patients without indication for surgery who only received medical treatment. In other words, to perform such an analysis, there is a need to exclude patients who should have been operated but were not.

Response:
We confess that this idea is fascinating but, nevertheless, feel that such an analysis is not really feasible for us at the present stage of the work. Considering the retrospective nature of this study, we do not believe that such study groups could be reliably identified based only on the case history. It is possible that there may have been a few patients who had indication for operation but were for some reason not operated on. Yet, we doubt whether such a classification could be unequivocally trustworthy based on the data of the hospital records. On the other hand, failure to record data in the hospital files indicating the need for operation in the conservatively treated patients does not undeniably exclude such a possibility.

Comment 2.
The Reviewer suggests that we should comment on the percentage of losses during follow-up.

Response:
The number of the patients included and evaluable at each time period can be seen in Figures 1, 2 and 3. For example, the number of patients evaluable after a follow-up of 10 years is noticeably larger than the number of patients evaluable after a follow-up of 15 years. This is not due to losses during the follow-up but reflects the difference in the follow-up time of various patients. Some of the patients with IE who were included during the early years of the study were followed for more than 20 years, while for a few other patients, the follow-up period was only a little more than one year.

We have addressed this point on page 6, lines 10-12 by presenting also the 25% percentile and 75% percentile of the follow-up time as follows: “The mean (SD) follow-up time for the 1-year survivors was 11.5 (7.3) years (range 25 days to 25.5 years), and the 25% percentile of the follow-up time was 4.8 years and the 75% percentile of the follow-up time was 17.8 years.”
Comment 3.
The Reviewer suggests that we should comment on the causes of mortality during follow-up and if they were related to endocarditis or not.

Response:
This has been done on page 6, lines 18-21 (revised manuscript) by stating “A total of 94 patients died during the follow-up. The causes of death were: recurrent IE (n=1), sequelae of IE (n=27), coronary heart disease (n=18), malignancy (n=16), infection other than IE (n=14), stroke (n=6), other or unknown cause (n=12).

Comment 4.
The Reviewer suggests that we should discuss why long-term mortality among survivors was lower in patients operated on because of heart failure.

Response:
There must be some misunderstanding here. In fact, in the original manuscript, it was survival, not mortality, that was lowest for the patients who were operated on for heart failure. Also in the revised manuscript, survival among the one-year survivors was lowest for the patients operated on for heart failure.

Comment 5.
The Reviewer finds it sticking that patients with recurrent episodes of IE had significantly lower mortality rates than those with no recurrences, and recommends that we should discuss this finding.

Response:
At least a partial explanation for this could be that intravenous drug use was a risk factor for the recurrences of IE. The patients with intravenous drug use had a significantly lower mortality than those with no drug use, evidently due to the fact that they commonly had tricuspid valve IE with low mortality.

Comment 6.
By this comment, the Reviewer brings it out that he/she finds some of our findings unexpected. He/she focuses attention on the fact that heart failure was the most powerful predicting factor of long-term mortality, and wonders why only 17 patients needed surgery after one year of the episode of endocarditis.

The Reviewer also asks what were the indications of late valve surgery?

Response:
It is true that heart failure was a powerful predictor of long-term mortality in our patients and yet, only 17 patients underwent the first cardiac operation more than one year after the initial episode of IE. These results are not contradictory since in the present study, we analysed the association between the patient characteristics during the initial episode of IE and the long-term outcome of the patients. Consequently, statistical analyses involved the association between heart failure within 3 months of admission and long-term mortality.
To fulfil the Reviewer’s requirement, we have presented the indications for late valve surgery on page 9, lines 14-16 (revised manuscript) as follows: “Altogether 20 patients underwent late valve surgery. The indications for late valve surgery were: valvular regurgitation without heart failure (n=15), dehiscence of prosthetic valve (n=3), valvular stenosis (n=1), and heart failure (n=1).

We must admit that we do not quite understand what the Referee means with the question, whether the patients with heart failure and valvular dysfunction were not operated on. They were, but this is probably not what the Reviewer means.

Comment 7.
The Reviewer focuses attention on the fact that we found early surgery to be associated with a requirement of late valve surgery.

Response:
We thank the Reviewer for focusing our attention on this awkward finding. It has led us to check all of our earlier results. An error was found in this particular point of our analyses. In fact, none of the clinical factors during the initial hospitalisation included in our multivariate analyses were associated with the requirement of late valve surgery. We have changed the text accordingly (page 9, lines 22-23). We apologize for this regrettable error.

Comment 8.
We have stated in the Discussion of our original manuscript that we regard the finding that the long-term survival was practically similar for the patients with and without neurological manifestations or peripheral emboli during the acute phase of their illness as somewhat unexpected (page 12, lines 1-4, original manuscript). The Reviewer, for his/her part, finds this finding to be quite expected, considering it logical that these complications do not influence the long-term prognosis.

Response:
We understand and appreciate the Reviewer’s opinion. Moreover, when only the patients who survived one year were included in the analyses, there was no difference in mortality between the patients with or without neurological complications or peripheral emboli. We have changed the discussion as follows: “The results of the present study show that the long-term survival was practically similar for the patients with or without neurological manifestations or peripheral emboli during the acute phase of their illness (Table 1). This finding is not surprising, since once the patient has solved such an acute complication, it seems logical that it no longer influences the long-term prognosis.” (page 12, lines 4-8).

Discretionary Revisions (which the author can choose to ignore)
The main criticism of the paper is that a very heterogeneous group of patients with IE is included. The Reviewer feels that several patient groups should have been separately analysed because of different epidemiological, clinical, microbiological and echocardiographic characteristics.

The Reviewer also feels that the manuscript is not well structured, which makes it difficult to read and understand.

Further, the Reviewer asks in which group were the patients who were operated on between being discharged after the initial episode of IE and one year of the admission included.
Response:
We appreciate the Reviewer’s comment of the heterogeneous nature of our study population. However, at the present stage, it is not practicable for us to completely change the character of our work.

However, following the Reviewer’s suggestion, we have made efforts to improve the structure of the manuscript and make it more easily readable. A major revision has involved the study group: in the revised manuscript, only the patients surviving more than one year after the initial admission for IE have been included in the statistical analyses focusing on the long-term overall mortality and cardiac mortality. Already in our original manuscript, analyses regarding the late valve surgery involved only the one-year survivors. Recurrent episodes were analysed both for the one-year survivors and all 303 patients.

The answer to the question in which group were the patients who were operated on between being discharged after the initial episode of IE and one year of the admission included is that these patients were not included in the present work. This particular group of patients has been described by us in our previous paper describing the short-term and one-year outcome and requirement of surgery in the whole patient population (Heiro et al. BMC Infect Dis 2007, 7:7).

Reviewer 2 (Maurizio Cotrufo)
General:
The Reviewer feels that the main flaws of the paper reside in the exposition of early and late mortality data that somehow lacks clarity.

Major Compulsory Revisions
Comment 1.
The Reviewer feels that since the paper is centred on early and late mortality rates and predictors, it should have been more detailed in reporting e.g. how many patients were surgically treated, what criteria were adopted to choose between medical and surgical treatment at the first hospitalisation, what were the causes of death both in the hospital and during the long-term follow-up. In particular, the Reviewer is interested in the number of patients dying during the first hospital admission.

Response:
Many of these issues have been examined and reported in two of our previous papers focusing on: 1) the short-term and one-year outcome of these patients (Heiro et al. BMC Infect Dis 2007, 7:7) and 2) epidemiological changes of IE in patients treated for IE in a Finnish teaching hospital (Heiro et al. Heart 2006;92:1457-1462).

In this paper, the purpose was to report only on the long-term prognosis of these patients.

To describe some of our earlier results:

89 of all 303 patients underwent surgery during the initial hospitalisation, 94 patients underwent surgery during 3 months, and 109 patients needed surgery during 1 year.
The indications for surgery during 3 months were cardiac failure (n=55), valvular regurgitation without heart failure (n=43), dehiscence of prosthetic valve (n=10), intractable infection (n=6) and repeated emboli (n=5).

The in-hospital mortality was 14%.

We feel that it would not be appropriate to repeat these data in the present manuscript. However, we can do so, if wished by the Editor or the Reviewer. In contrast, we have made efforts to give a thorough description of the present study group (=one-year survivors) in the revised manuscript. This has been done on page 6, lines 6-21.

Comment 2.
The Reviewer points out that we had quite a high in-hospital mortality (> 20%), which should require data on whether this was due to medical treatment failures or surgical drawbacks. Moreover, since our multivariate analyses found early surgical treatment as an independent protective factor for mortality, it would be important to know the respective rates of hospital death among medically versus surgically treated patients.

Response:
We are sorry to say that we are not able to understand the grounds for the Reviewer’s statement regarding the high in-hospital mortality rate of >20%. In the present manuscript, we do not give any data regarding the in-hospital mortality. Yet, data regarding early mortality of these patients has been given in our previous work published in this Journal (Heiro et al. BMC Infect Dis 2007, 7:7). According to this paper, the in-hospital mortality was 14% (please, see above).

Data regarding the in-hospital mortality rates among the surgically treated patients and conservatively treated patients have also been given in this previous paper. No significant difference in mortality was found between these two groups (16.9% vs. 13.1%; p= 0.751). Again, we feel that it would not be appropriate to repeat these data in the present manuscript. However, we can do so, if wished by the Editor or the Reviewer.

Comment 3.
The Reviewer asks whether postoperative mortality was conditioned by the timing of intervention? In other words, besides being a predictor of long-term survival, was early surgery associated with better hospital outcome or not?

Response:
As stated above, we have compared the outcome of the patients undergoing early surgery with the outcome of those treated only conservatively in our previous paper ((Heiro et al. BMC Infect Dis 2007, 7:7). There was no statistically significant difference in the in-hospital mortality between the surgically and conservatively treated patients (see also above, please).

Comment 4.
The Reviewer requires about the causes of death (at least distinguishing between cardiac and non-cardiac causes).

Response:
The causes of death among the one-year survivors have been added on page 6, lines 18-21 (please, see also our response to Comment 3, Minor essential revisions, Reviewer 1).
Minor essential revisions

Comment 1.
The Reviewer suggests that follow-up completeness should be reported.

Response
The numbers of patients available and evaluable at each time point are given in Figures 1, 2 and 3. We have added the 25% percentile and 75% percentile of the follow-up time on page 6, lines 10-12. Please, see also our response to Comment 2, Minor essential revisions, Reviewer 1.

Comment 2.
The Reviewer comments on that Tables 1 and 2 are busy with data and questions whether they provide relevant information.

Response
The main findings have been presented in the text but exact numbers are seldom given. Therefore, we would prefer to preserve these two tables. Nevertheless, they can be omitted, if necessary.

Comment 3.
The Reviewer comments on that Figure 1 is not graphically correct. He recommends that only the overall population curve should be displayed.

Response
This observation is correct. In the revised manuscript, the fault has been corrected due to the fact that the study group involves only the one-year survivors.

Reviewer 3 (Raul Moreno)

We thank the Reviewer for his kind words regarding the general interest of our paper.

Comment 1.
The Reviewer points out that it would be interesting to provide the data not considering all the 326 episodes, but only the 303 first episodes of endocarditis.

Response:
We have followed the suggestion of the Reviewer and performed the statistical analyses regarding the long-term and cardiac mortality also for only the first episode of IE in each patient. The number of the episodes included was, however, not 303 but 243, since following the requirement of Reviewer 1, only the patients surviving over one year were included.

The results regarding these first episodes of IE have been added in the text. The findings did not differ regarding the long-term overall survival (page 7, lines 26-27, page 8, lines 1-3). Regarding the cardiac mortality, heart failure was a significant risk factor in multivariate analysis among all 243 episodes, but the association did not quite reach statistical significance, when the repeated episodes were excluded (page 9, lines 2-5).
Comment 2.
The Reviewer recommends that the concrete causes of death could be provided.

Response:
As stated above, the causes of long-term (>1 year) deaths have been added in the revised manuscript (page 6, lines 18-21). Please, see also our response to comments of Reviewer 1 and 2.

Comment 3.
The Reviewer suggests that in the Discussion, a paragraph trying to explain the prognostic implications of collagen disease should be included.

Response:
Collagen disease was found to be an independent risk factor for mortality even when only the patients surviving over one year were included in the analyses.

Following the recommendation of the Reviewer, we have added the following speculation in the Discussion section:
“In the patients with collagen disease, the severe nature of the underlying disease may have contributed to high mortality. Of all 9 patients with collagen disease, who died during the follow-up, 3 needed chronic dialysis, 1 had nephrotic syndrome and in 3 patients, the cause of death was a malignancy” (page 11, lines 16-19).