Author's response to reviews

Title: Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004

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Dr Chrissie Kouremenou  
Senior Assistant Editor  
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Dear Madam,

Thank you for your positive letter regarding our manuscript MS: 1081487658126031 entitled “Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish Teaching Hospital during 1980-2004 ” by drs. Maija Heiro, Hans Helenius, Saija Hurme (born Mäkilä), Timo Savunen, Erik Engblom, Jukka Nikoskelainen, and myself. We were pleased to receive a request of a revised version of this manuscript. We found the criticism and comments presented by the Reviewers constructive, and feel that they have helped us to improve the manuscript. The manuscript has now been revised according to these suggestions. We include here a detailed list providing point-by-point responses to all of the Reviewers’ comments and indicating the changes made according to their suggestions.

During the new analyses, we observed an error in our previous numbers regarding the surgical treatment. The numbers have now been corrected. This caused only minor changes in the results, although the numerical data in Table 5 was changed.

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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Reviews on the criticism presented by the Reviewers and a list of the changes made according to their suggestions.

Reviewer 1 (Peter AP Wilson)

Major Compulsory Revisions

Comment 1.
The Reviewer is concerned about the fact that the tables of the manuscript do not indicate the number of cases with missing information.

Response:
The number (N) of cases with the analysed variables at the beginning of the study is given in Table 1. A total of 326 episodes of infective endocarditis (IE) were analysed for all clinical characteristics except for the laboratory parameters. Among the laboratory parameters taken on admission, serum C-reactive protein (CRP) -value was available in 272 episodes, erythrocyte sedimentation rate was available in 192 episodes, and serum creatinine value was available in 282 episodes. Regarding the clinical characteristics, the missing data during the follow-up was only due to the death of the patients. As shown in Table 1, a total of 53 patients died within one year. Thus, at the time point of 1 year, a total of 250 patients were alive and evaluable.

We have added in Table 1 that data regarding the CRP value on admission was available in 272 episodes and data regarding the serum creatinine value on admission was available in 282 episodes. Similarly, we have added in Table 2 that data regarding erythrocyte sedimentation rate on admission was available in 192 episodes.

Comment 2.
The Reviewer points out that some of the methods, e.g. the CRP method, may have changed during the study period.

Response:
It is evident that during the long study period of 25 years, there must have been changes in the diagnostic methods of infective endocarditis (IE). Although it is not possible to accurately evaluate, how such changes may have affected some of the results, this is a very important issue and should be addressed in the Discussion section. Therefore, we have added in the end of the Discussion section a new chapter including a statement that the potential impact of these changes poses one limitation of the study.

Please, see also response to Comment 1, Reviewer 2.
Comment 3.
The Reviewer notes that instead of the P value of 0.05, a P value of 0.01 may be more appropriate in multiple comparisons.

Response: The correction of the p-values for multiple comparisons is most often applied in the analysis of variance (ANOVA) when several post-hoc comparisons are done for the same response variable. There is a large spectrum of correction techniques for ANOVA depending on the formulation of the post-hoc questions. In our case, the corrections would mean corrections for the number of the different response variables and in our case, the only possible correction technique would have been the Bonferroni’s method. In this method, the correction is done by multiplying each unique p-value by the number of all tests. In our opinion this would have led to enormous underestimation of the significances. Also in a philosophical sense, we do not find this fruitful. Each response variable was analysed separately without any multiple comparison corrections according to the number of variables. This is general practice and we would prefer to do so. Different response variables in the study are describing separate aspects of the results. By multiplying the p-values with the number of analysed variables would lead to ultra-cautiousness and to hiding of a lot of relevant findings.

Comment 4.
The Reviewer recommends that the completeness of the follow-up at 6 months and one year needs to be better described.

Response:
Data on mortality within 6 months and 1 year were primarily collected from the hospital records. However, it is possible that after discharge of the initial hospitalisation, the patient may have died in some other hospital of our region, or even at home. Therefore, in addition to the hospital records, dates of possible deaths were also obtained from the National Population Registry, in which all deaths and causes of deaths of the Finnish residents are registered.

Data on the surgical treatment within 6 months and 1 year was collected from the hospital records of the Turku University Hospital. This was feasible, since as the tertiary care facility for the south-western part of the country, Turku University Hospital is in our region the only hospital, in which cardiac surgery is performed.

We have added in the Materials and Methods section the following sentence: “In addition to the hospital records, dates of possible deaths were obtained from the National Population Registry, in which all deaths and causes of deaths of the Finnish residents are registered.”

(page 4, lines 11-13)

Comment 5.
The Reviewer points out that it is surprising that the need for surgery was independent of the organism, especially Staphylococcus aureus. He further asks, whether the lower rate of surgery in patients with high erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) were related to early death.

Response:
We agree with the Reviewer that is somewhat surprising that Staphylococcus aureus did not result in earlier surgery. This may have been associated with the fact that 20 of the 75 cases of Staphylococcus aureus IE were in patients with IVDU, of whom 15 had tricuspid valve IE with no surgery.
As to the second question, we have analysed the hazard ratio for in-hospital death among the surgically and conservatively treated patients with high and low serum CRP values on admission, as well as with high and low ESR values on admission. Among the surgically treated patients, the hazard for in-hospital death for the patients with CRP values $\geq 100$ mg/l on admission was 6.85-fold as compared to those with CRP values $< 100$ mg/l on admission (HR 6.85, 95% CI 1.51 to 30.95; p = 0.013). Among the conservatively treated patients, no significant association was observed between in-hospital mortality and the level of CRP on admission (p= 0.181). When analysed separately for the surgically and conservatively treated patients, no association was observed between the level of ESR on admission and in-hospital mortality (p values > 0.468).

These data have been added in the text of the revised manuscript.

(page 9, lines 11-17)

**Minor essential revisions**

**Comment 1.**
The Reviewer feels that the Discussion is too long and recommends that it should be shortened by one third.

**Response:**
Following the recommendation of the Reviewer, we have made efforts to shorten the discussion, but it has been difficult. In so doing, we have deleted e.g.

- data on the serum creatinine concentration used by Wallace at al. in their study focusing on prognostic factors of in-hospital and 6-month mortalities (*Heart* 2002, **88**:53-60).
- chapter dealing with *Streptococcus pneumoniae* IE (page 9, chapter 3, original manuscript).

However, to satisfy the requirements of Reviewer 2, we have added a few new points in the Discussion section. Therefore, the revised Discussion is not really shorter than the original one. We hope that this meets the Reviewer’s approval.

**Comment 2.**
The Reviewer recommends that “significantly dependent of” should be rephrased.

**Response:**
This has been done. Instead of “significantly dependent of”, we use the phrase “significantly associated with” throughout the revised manuscript.
Reviewer 2 (Michel Wolff)

Comment 1.
The Reviewer points out that a very long time period elapsed between the first and the last patient, and that during such a long period of time, several aspects of diagnostic and therapeutic management may have changed significantly.

Response:
We agree with the Reviewer in that the study period was long and that it may have somewhat affected the results. On the other hand, since IE is an uncommon disease, the long study period has made it possible for us to collect a considerable number of patients with IE. Also Reviewer 2 has focused attention on the issue of potential changes during the study period. We have taken the considerations of both of the Reviewers into account and address this point in the revised Discussion section as follows:

"Although IE is an uncommon disease, the long study period of 25 years made it possible for us to include in this study a considerable number of patients with IE. It is of concern, however, that during such a long period of time, there may have been changes in several aspects of diagnostic and therapeutic management of IE. This is evidently one limitation of the present work."

(page 12, lines 24-27)

Comment 2.
The Reviewer feels that the paper would be strengthened if we include only the episodes of definite IE according to the Duke criteria.

Response:
After careful consideration, we would prefer to maintain the patient population studied as it is. If only the 224 episodes of definite IE were included in this study, the whole manuscript would be changed, since we would need to re-perform all the analyses. Moreover, we would practically have to re-write the text and the tables of the manuscript. In fact, we feel that it would not involve a revision but, rather, preparing of a new and different manuscript.

Moreover, many of the important studies (e.g. Cabell et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002;162:90-94; Chu et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745-1749) focusing on the predictors of clinical outcome in IE, to which we refer to in the present manuscript, have included both definite and possible cases of IE.

Comment 3.
The Reviewer points out that IE is not a homogenous disease and considers that the left-sided IE, right-sided IE and prosthetic valve IE are probably different disease entities. Therefore, he recommends that these subgroups of patients should be analysed separately, at least patients with left-sided and those with prosthetic valve IE.

Response:
As requested, we have performed such an analysis evaluating the outcome separately for the patients with left-sided IE and prosthetic valve IE. The result was that there were no significant differences in the outcome between these two groups during the different follow-up periods (initial hospitalisation, 3 months, 6 months, and 1 year from the admission (p values between 0.737 to 0.934).
Comment 4.
The Reviewer recommends that more information should be given on the number of patients who underwent only TTE and those who had also TEE. He also points out that there is no information about the size of the vegetations.

Response:
Transthoracic echocardiography (TTE) was performed in all episodes of IE, followed by transesophageal echocardiography (TEE) in 184 episodes. The proportions of patients having only TTE, or both TTE and TEE, varied during the different study periods: the proportion of patients having TEE was 4.9% between 1980-1985, 33.3% between 1985-1989, 76.9% between 1990-1994, 88.3% between 1995-1999, and 66.3% between 2000-2004. A major echocardiographic criterion was demonstrated by TTE in 30 (93.6%) of the 32 episodes between 2000 and 2004, in which only TTE was performed.

This information has been given in our previous paper (Heiro M, et al. Heart 2006;92:1457-1462). Therefore, we feel that it should not be appropriate to repeat the data in the present manuscript. However, we understand the relevance of the Reviewer’s comment, and have added the sentence “Transthoracic echocardiography (TTE) was performed in all episodes of IE, followed by transesophageal echocardiography (TEE) in 184 episodes.” in the text of the revised manuscript. (page 6, lines 4-5).

Unfortunately, the size and mobility of vegetations were not recorded in this study. We have referred to this fact in our Discussion section (page 11, lines 25-26).

Comment 5.
The Reviewer points out that many previous papers have identified neurological complications as factors associated with a worse outcome. To improve the manuscript, he recommends that we should analyse, whether different complications, e.g. ischaemic stroke, cerebral bleeding or meningitis, play a similar role in the outcome.

Response:
As requested, we have performed such analyses. There were no statistically significant differences in the outcome between the patients with different neurological complications (embolic brain infarction, brain haemorrhage, transient ischaemic stroke, meningitis) (p values between 0.737 to 0.934). These data have been added in the revised manuscript (page 6, lines 19-22).

Comment 6.
The Reviewer feels that short-term and long-term outcome could be more interestingly presented as Kaplan-Meier survival curves.

Response:
Here we feel somewhat differently, since an abundance of figures would be needed to present the data presented in the tables of the manuscript. Therefore, we would to prefer to provide this information in the tables. However, it the Reviewer and the Editors feel that this is a crucial point, we are ready to satisfy this requirement and produce the many figures. Nevertheless, we would be pleased to preserve also the tables.
Comment 7.
The reviewer rightfully claims that the role of cardiac surgery as a prognostic factor is very complicated. Patients may not be operated on because they are critically ill while some patients undergo cardiac surgery only because they have large vegetations. The Reviewer feels that the best way to evaluate cardiac surgery is to perform a nested case control-study with a propensity score. This type of analysis has already been performed for left-sided complicated valve IE (Hasbun et al. JAMA 2003).

Response:
Unfortunately, we have to admit that we have not been able to produce this type of a statistical analysis in the patients included in this study. Since surgical treatment forms only a rather small part of the present work, we believe that such an analysis may not be crucial for its contents. We hope that this will meet the Reviewer’s and the Editors’ approval.

However, we appreciate the issue raised by the Reviewer on the complicated nature of the surgical treatment as a prognostic factor of IE. Consequently, we feel that this fact should be more clearly noted in the Discussion section. To do so, we propose a new beginning for the chapter dealing with the surgical treatment of IE, in which this problem is brought out (page 12, lines 12-14). After that, we describe the facts, which we believe to be the main reasons, why mortality was here somewhat higher for the surgically treated patients than for those treated conservatively. In short, the patients who underwent surgery had a more severe disease, illustrated by a higher frequency of complications (heart failure, neurological complications, peripheral emboli), all of which per se were shown to significantly predict mortality in our patients.

Comment 8.
The Reviewer points out the role of serum C-reactive protein is interesting but considers the clinical relevance of this finding unclear. He recommends a ROC curve with the 100 mg/L cut-off, in order to strengthen the result.

Response:
We have analysed the data using survival analysis by applying Cox’s regression analysis. This well known technique is based on observation of time to some event. This methodological approach allows censored observations (time observations without the event). It is a more powerful technique than logistic regression analysis in the situation where there are censored observations (Hosmer and Lemeshow: Applied Survival Analysis, Regression Modeling of the Time to Event Data, 1999, John Wiley & Sons, INC, New York). The ROC analysis with ROC curve is enclosed with logistic regression analysis in which analysis of the censored observations are excluded from the calculations. We would prefer not to do the analysis using a method, which is not as powerful as the method we have used.

Comment 9.
The Reviewer considers the finding that no significant difference was observed in the outcome between Staphylococcus aureus IE versus other pathogens unusual, and wishes that this specific finding should be commented on.

Response:
We totally agree with the Reviewer at this point and have made efforts to discuss this finding in the manuscript (page 11, lines 4-6, revised manuscript).

In the present study, 20 of the 75 cases of S. aureus IE were in patients with IVDU. Of these patients, 15 had tricuspid valve IE with no mortality. We believe that this may have contributed to the fact that the outcome of S. aureus IE was not significantly worse than the outcome of IE caused by other microorganisms.
Comment 10.
Mortality and need of surgery was higher for those patients who had infections of 2 native valves. The Reviewer suggests that this might be a consequence of the sole aortic infections, since aortic valve IE was associated with a worse outcome and more surgery.

Response:
We must confess that we do not quite understand what the Reviewer means with this point. Based on Table 1, for example, mortality of aortic valve IE does not appear to be very high as compared to the other valve types. However, of the 32 cases with infection of 2 native valves, 30 involved the aortic valve. According to our interpretation, this means that when there is a combination of an aortic valve infection and an infection of a second valve (usually the mitral valve), then the mortality is high. Admittedly, the need for surgery in the sole aortic valve disease was high.

Comment 11.
The Reviewer comments that most of the data in this series has already been published by us in earlier papers.

Response:
We must say that we cannot share the Reviewer’s opinion in this. Although the patients included in the present study are the same as those in our preceding work (Heiro M, et al. Heart 2006;92:1457-1462), the data analysed and given in the present manuscript are different. In that previous work, specific attention was focused on the changes of the clinical characteristics within 5-year study periods during 25 years. When the outcome and the need for surgery were analysed, the duration of the follow-up was 3 months from the admission. In the present work, the attention was focused specifically on the factors predicting the outcome of IE, and when the outcome and the need for surgery were analysed, the durations of the follow-up were 1) initial hospitalisation, 2) six months and 3) one year from the admission. In the present work, we also evaluate the association between the clinical characteristics of IE and the development of complications during the initial hospitalisation.