Author's response to reviews

Title: Cardiovascular risk management in patients with active Ankylosing Spondylitis: a detailed evaluation

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Object: BMC Musculoskeletal Disorders MS: 2030390628142657 - Cardiovascular risk management in patients with active Ankylosing Spondylitis: a detailed evaluation

Dear Editor,

We thank the reviewers for their comments, which we have taken into account in our revised manuscript. Please find enclosed our reply to the points and questions raised by the reviewers of our manuscript.

We would highly appreciate your reconsideration for publication of this manuscript in BMC Musculoskeletal Disorders.

Yours sincerely,
Also on behalf of the co-authors

Sjoerd Heslinga and Michael Nurmohamed
Associate Editor
When you specify the New York criteria for AS, do you actually mean the modified New York criteria? They aren’t identical, in specifying the 1984 criteria you imply the modified criteria, this needs to be corrected if this is the case. All abbreviations in the text, tables and figures need to be defined.
The modified New York criteria were used. The word “modified” was added in Methods, paragraph 1. All abbreviations throughout the manuscript were checked and replaced, or added were needed.

Minor corrections and typos were corrected throughout the manuscript. The references were adjusted to match the journal style.

Reviewer #1 (Dr. Sveaas)
Major Compulsory Revisions
1. Aim of the study - The first and the second aim of the study is clearly defined and well answered in the manuscript. However, although the third aim of the study at line 117-120 is clearly defined, I am not sure whether this aim is fairly answered in the manuscript due to lack on information regarding the duration of the treatment period and compliance with the prescribed treatment.
We agree with the last statement of the reviewer, as due to the retrospective cross-sectional design of the study, we were unable to report data about CV-RM medication compliance. However, we feel that the third aim has been achieved, as the described data gives an overview of current CV-RM and reaching of treatment targets in a cohort of patients with AS. In the future, with new data from these cohorts we might be able to answer the remaining questions on compliance.

2. Methods - The manuscript is based on data from a clinical setting, and maybe due to this the manuscript lack descriptions of some procedures. Second paragraph: More details about procedures for blood pressure measurements for the patient group should be added to the manuscript. If this is not available it should be stated that this was done in accordance with general procedures at the hospital.
We added the following sentence to Methods, paragraph two: “Blood pressure was measured manually according to the standard hospital procedures.”

3. Methods - Fifth paragraph: What was the time period between the first and the second visit for patients that received CV risk management? For example for patients with increased risk, when was it stated that these patients did not meet the treatment goals? And how was the follow up for these patients? And did you register compliance with treatment?
As mentioned under remark #1, we assessed CV-RM at a single moment in time. In the current study no interference regarding CV-RM was done. In the future, active treatment of increased CV risk should be studied in a prospective study.

4. Results - Result section, paragraph two. I think more information about the general population should be added to the manuscript, especially since the references that is cited for this only is available in Dutch (reference 13 and 14). A table
describing prevalence of CV-risk factors in the general population compared with
the patient group would have been informative in this manuscript. Although figure 2 partly
gives this information, I think some information about the exact values in
AS patients compared to the general population would have added valuable
information to the manuscript (if it is available for the general population).
Data, when available, about the general Dutch population has been implemented in figure 1.
We feel that through use of bar-diagrams, the differences between the AS population and the
general population are more easily readable compared to a table. The references were
adjusted, as advised by the last remark of the reviewer.

5. Results - Result section, paragraph 2. Why are BMI and prevalence of overweight not
compared to the general population?
BMI and the prevalences of overweight were not compared as no mean overweight
percentage was available for the general population, only per age category (figure 1).

6. Discussion - Discussion section, paragraph one. When summarizing the results I think it
should be specified that the results are valid for patients with high disease activity.
We added the following words to the last sentence of Discussion, paragraph one: “patients
with active”

Discretionary Revisions
1. References - Please consider to give more detailed web addresses for reference 13 and
14.
Both references were adjusted accordingly.

Reviewer #2 (Dr. Papagoras)
Major Compulsory Revisions:
1. Introduction - In the Introduction section, a reference to the EULAR CV-RM
recommendations (not guidelines) should be added. Ref 9 (J Rheumatol. 2010
Jan;37(1):161-6) better supports the statement “In recent years, however,
accumulating evidence for the increased CV risk in AS is emerging” and should
be moved after that.
We added a reference to the EULAR CV-RM recommendations (reference 9). Also, we
moved the former reference 9, now reference 12, to the suggested sentence.

2. Methods - In the “Study population” paragraph, the design of the study and the main
eligibility criteria must be clearly stated. Apparently, this is a retrospective
cross-sectional study, i.e. all patients were assessed for CV risk factors and
management at a single defined time point (right before anti-TNF treatment
initiation, when the disease activity was high). Moreover, all patients seem to
have been anti-TNF-naive. Dates of the assessment of the first and last patient
should also be provided. Why were etanercept and adalimumab the only options
for the subsequent anti-TNF treatment? Had the patients some kind of a trait that
excluded the administration of infliximab, golimumab or certolizumab? If not, the
We added the following sentence to Methods, paragraph 1: “This cross-sectional study was conducted retrospectively.” We also added the following words to paragraph 1: “TNF-α blocking therapy naïve”. Furthermore, the reference to etanercept and adalimumab was deleted: “(either etanercept or adalimumab)”. Data on the date of inclusion of the first and last patients was already provided in the Methods section, paragraph 1.

3. Methods - In “Patient characteristics” replace “length” with “height”.
The word “length” was replaced by “height”.

4. Methods - In “CV risk assessment” a reference to the Dutch CV-RM guidelines should be added.
A reference to the Dutch CV-RM guidelines was added.

5. Methods - In “CV risk management” the parameters taken into account in the Dutch CV-RM guidelines should be mentioned briefly and the guidelines themselves be referenced. Please, provide a definition for “smoker”.
A reference to the Dutch CV-RM guidelines was added. Also, we added the following sentences to Methods, paragraph 5: “gender, age, smoking status, SBP”, “Smoking is defined as current smoking.”

6. Results - In the “Prevalence of CV risk factors” paragraph the comparisons of the prevalence of the various risk factors between AS patients and the general population may lead to unsound conclusions, since both populations are not matched regarding gender and age distributions. Such a comparison should at least be age- and sex- adjusted. The results shown on Figure 1 are accompanied by no figure legend, colour legends, titles in the axes, percentages, p-values or other statistics and therefore are not at all informative.
Legends, titles and further clarifications were added for both figures, as these were unfortunately not processed in the final PDF. We do agree with the reviewer that age and gender adjusted comparisons are most valuable when comparing the presence of cardiovascular risk factors. However, age and gender adjusted data were not available. We think that a proper comparison can be made by the data that is available, as these data were collected from the Dutch general population in several large cohorts. We do agree that a future study should be designed which includes an age and gender adjusted control group to give further support for the findings in our study.

7. Results - In the “CV risk assessment” paragraph, it should be added that 8 patients were also excluded because of a prior diagnosis of a CV disease. In the same paragraph it reads that, after adding 15 years to the age of the AS subjects, 239 patients’ CV risk could be estimated. However, if 8 patients are excluded due to missing blood pressure or serum lipid data and another 8 patients due to prior CVD, that makes 254-8-8=238 evaluable patients.
The following sentence was added to Results, paragraph 3 “eight patients due to a history of CVD”. The last part of the paragraph was clarified by adding the following sentence:
“(excluding seven patients due to age below 40 years, eight patients due to CVD history, eight patients due to lack of data)”

8. Results - In the “CV risk management” paragraph, it reads that nine patients were not treated at all and 22 were under-treated. However, this is in conflict with the data in the following paragraph (“51 patients had an indication for CV risk treatment of which 47 patients (92%) received some form of CV risk medication”), as well as with Figure 2, in which it is shown that 4 patients were not treated and 27 under-treated. Overall, this whole paragraph should be re-structured according to the flowchart of Figure 2. Figure 2 should have a legend and be cited in the text. The text was corrected and reads now as following: “In total, of the 138 AS assessed patients, 51 patients had an indication for CV risk treatment of which 42 patients (82%) received some form of CV risk medication (figure 2). However, 39 (76%) of the 51 patients were treated inadequately due to failure to reach treatment targets for hypertension or hypercholesterolemia or due to total lack of CV risk medication (table 2).” The flowchart was corrected accordingly, and a citation to the flowchart was added in Results, paragraph 4. A legend for figure 2 was added.

**Minor Essential Revisions**
9. Introduction Section, second paragraph, first line: add “risk” after “CV”. The word “risk” was added.

**Discretionary Revisions**
10. In the Discussion section, the authors could provide data about the rates of successful CV-RM guidelines implementation in the general Dutch population, if available. How often are people of the general Dutch population treated appropriately for CV risk, undertreated or not treated at all? This could allow some thoughts concerning all those issues possibly interfering with CV risk management in people with rheumatic diseases mentioned in the fifth paragraph. To our knowledge, no data has been published on (under)treatment of cardiovascular risk in the general Dutch population and therefore this could not be discussed.

**Minor issues not for publication**
11. Discussion section, fifth paragraph: after “76%” delete “percent”. The word “percent” was deleted.

**Reviewer #3 (Dr. Gonzalez-Gay)**
1. Please, state (whether applicable) that the results on BASDAI (mean 5.9) shown in Table 1 were obtained prior to the onset of anti-TNF therapy. In the Methods section we added the following sentence to paragraph one, as also mentioned by reviewer #2, remark 2: “TNF-α blocking therapy naïve”

2. Introduction: To emphasize the higher frequency of subclinical atherosclerosis found in AS patients when compared with controls, discuss a study that disclosed increased risk of subclinical atherosclerosis, including a higher frequency of carotid plaques in patients with
AS without clinical history of cardiovascular events compared with matched controls. Use for this purpose the following article published by Gonzalez-Juanatey et al in Medicine Baltimore in 2009 (Gonzalez-Juanatey C, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. Medicine (Baltimore) 2009 Nov;88(6):358-65). This article might be used as reference 10 in the revised manuscript.

In the introduction this additional reference was added (reference 11), as suggested by the reviewer.