Author’s response to reviews

Title: Cardiovascular Co-morbidity in Patients with Rheumatoid Arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment

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Author’s response to reviews:

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December 15, 2017

Dear Dr. Mock

Thank you for consideration of our manuscript BRHM-D-17-00022, “Cardiovascular Co-morbidity in Patients with Rheumatoid Arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment.” We have carefully considered all suggestions and comments by the reviewers and editor and made changes accordingly. We appreciate the valuable comments by the reviewers as well as the references provided by them. We think that these revisions have improved significantly the quality of this manuscript. We hope that with these modifications, the manuscript will be now suitable for publication in BMC Rheumatology. Thank you for reconsideration of our work.

Sincerely,

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Reviewer #1:

General Comments

Comment: CVD is RA has been in the forefront of research in the last few decades possibly due to the contribution of the inflammatory load and its links with various different classical CVD risk factors. So the review is timely and the authors have done well, in parts of the paper, to discuss very good quality evidence from systematic reviews and meta-analyses. However, overall there are other statements that are not supported by the current literature and stronger evidence is required to support some statements (or at least discuss issues with better transparency).

Response: We have changed wording of several sentences and added newer reference, including clinical trial studies for better presentation of available evidence.

Comment: This is a narrative review and thus will always be prone to bias, given that PRISMA guidelines and risk of bias has not been utilized to discuss the quality of the included studies. These limitations have to be discussed in more detail in the review.

Response: We have addressed this point made by the reviewer at the end of the introduction. The format of the journal does not include a discussion section where we could elaborate more on this point. Therefore, we addressed the major limitations that a narrative review has over a systematic review by adding the following sentence at the end of the introduction:

“This narrative review summarizes current data about CVD risk in patients with RA, the status of current CVD risk prediction models, and discusses management to reduce this risk. As such, this narrative review does not address risk of bias of the articles included and it may not have taken into consideration all the available data as a systematic review would have done.”

Comment: In addition to this, there are typos and grammatical errors and I think that the review needs another look to amend these issues.

Response: Thank you pointing out these errors. We have revised the manuscript thoroughly and had it edited by a language editor.

Comment: Finally, increasing physical activity and fitness are two different things that contribute as a classical CVD risk factor in the overall CVD burden we see in RA. There are studies showing significant associations of physical activity and cardiorespiratory fitness with CVD
outcomes as well as trials on the same subject. There are excellent Cochrane meta-analyses as well as other meta-analyses on exercise and RA, demonstrating positive effects. Furthermore, EULAR now advises the use of physical activity/exercise as an adjunct treatment for managing CVD in RA. As such, this has to be discussed in the paper alongside all the other classical CVD risk factors, particularly because increasing physical activity and fitness can improve other CVD risk factors (excellent meta-analyses on insulin resistance, blood pressure, inflammation etc).

Response: Thank you for this very important point. We have reviewed the literature again and found cross sectional studies that showed association of physical inactivity with worse CVD profiles. Those references have been added to the updated manuscript. There are several studies on benefits of exercise in RA but not specifically with CVD outcomes (Cochrane review). A recent clinical trial showed benefit of exercise program on endothelial dysfunction and we have added that reference. All of these references have been added to the manuscript and the importance of cardiopulmonary fitness as a way of decreasing CVD risk. Below is the modified text.

“Physical inactivity is associated with higher risk of myocardial infarction in the general population according to the INTERHEART case–control study. Data from 33 large prospective cohorts demonstrated a 35% relative risk reduction in CVD related death associated with being physically active. Unfortunately, several studies indicate that patients with RA are frequently inactive. This is partly due to pain and fatigue, lack of motivation, and lack of patient understanding of the negative impact of physical inactivity. A recent meta-analysis showed that CVD morbidity was not increased with physical inactivity among RA patients (RR 1.00, 95% CI 0.71-1.29). However, the results must be interpreted with caution because this meta-analysis included only two studies, both of which had cross sectional designs. A cross sectional study examined the impact of physical activity on CVD risk profile in RA patients. Levels of physical activity were assessed in 65 patients using a questionnaire. After adjusting for age, weight, sex and smoking status, and RA disease activity, physically active patients with RA had significantly lower systolic blood pressure, cholesterol levels, low density lipoprotein, homocysteine, Apolipoprotein B, von Willebrand Factor, and Type-I plasminogen activator inhibitor antigen. This suggests that CVD risk profile of patients with RA can be improved by implementing increased physical activity. Data from a systematic review of randomized clinical trials of exercise programs among patients with RA showed that exercise improved aerobic and muscle strength among these patients. The benefit that these aspects have on decreasing CVD risk still requires more direct and specific evaluation since none of these trials evaluated this relationship. There is accumulating clinical data that shows improved CVD risk parameters with exercise in RA. Forty patients with RA were divided into an exercise group who received 6 months of tailored aerobic and resistance exercise and a control group who received only information of exercise benefits. Significant improvement in the endothelial function parameters was noted in the exercise group compared to control group. This suggests that exercise may reduce CVD risk by impacting endothelial dysfunction, though long-term effect of exercise intervention on this parameter needs further evaluation. Other studies showed that exercise...
can reduce CRP levels[119] and has an anti-atherogenic effect, which suggest how exercise can impact CVD risk.[119, 120]

Cardiopulmonary fitness is measured by the maximal oxygen uptake (VO2max) test. Low levels are associated with high risk of cardiovascular disease and all-cause mortality. [121-123] It has been reported that patients with RA have low cardiopulmonary fitness. [121] A recent cross-sectional study evaluated the association of VO2max with CVD risk in the RA population. [124] Results showed that patients with RA not only had lower VO2max levels, but also that those with higher levels of VO2max had better cardiovascular risk profiles. There is evidence that cardiopulmonary fitness in RA can be improved with aerobic and resistance exercise intervention; thus, providing an exercise program to patients with RA is a useful tool to attenuate CVD risk. [125] Based on current evidence, RA patients should be encouraged to exercise not only to improve physical function but also to reduce cardiovascular disease.

Introduction

Comment: The references 2-4 are not strong and actually are reviews on the links between inflammation and atherosclerosis. This does not necessarily mean that inflammation causes atherosclerosis in RA. At least, clarity is required in this sentence (and correction of the typos)

Response: Thank you for the comment. We agree with you statement. We have removed the above-mentioned references and added newer stronger references (2-12 in the manuscript) to the introduction. We agree that causation of inflammation and atherosclerosis is not proven and current data just suggests an association. The wording of the text has been changed to reflect the same.

“Compared to the general population, a considerably higher risk of cardiovascular disease (CVD) is seen in patients with RA.[2-4] Hyperlipidemia, diabetes mellitus, family history of CVD, and body mass index are the risk factors associated with CVD risk in these patients.[5] Previous studies indicated that these traditional CVD risk factors do not fully explain the increased CVD risk among RA patients.[6] For example, a prospective cohort study of 114,342 women participating in the Nurses' Health Study found >2-fold higher risk of myocardial infarction in women with RA compared to non-RA, even after adjusting for cardiovascular risk factors.[7] This data suggests that RA related factors, possibly inflammation, is associated with the increased CVD risk that exists in this population.[8-12] Thus, adequate control of RA disease activity as well as management of CVD risk factors are needed to mitigate the heightened CVD risk that exists among patients with RA.”

Comment: Please reference each CVD risk factor accordingly with good quality studies. If you cannot find good RCT and/or meta-analyses then discuss this accordingly

Response: We agree with this comment. We included information as much as we found, from clinical trials. However, in some topics only longitudinal data was available. We then delineated throughout the manuscript the type of study design cited in the topic to show the level of evidence available.
Comment: Do we have enough data to suggest that we need to make priority the management of CVD risk factors? Which ones are the more important than others, based on the data that we have available?

Response: There is data that support that controlling RA disease activity is associated with decrease in CVD risk. However, there is now data available that supports that managing traditional risk factors such as hyperlipidemia, also decreases the risk for CVD events. The management of these factors should follow the guidelines of the general population. There is no data in support that modifying one traditional risk factor over another (hyperlipidemia (first) over hypertension (second)), has any increased benefit in reducing CVD risk. Hence, the recommendation remains to manage the CVD risk in these patients based on the CVD primary prevention treatment guidelines for the general population. We modified the manuscript to reflect these points.

Mortality

Comment: There is a lot of assumptions in the 2nd paragraph. I do not actually think that based on the available studies we can conclude that mortality declines? We need to highlight the need for further research in this field and better studies that can have enough follow up and event to develop further our understanding about these associations. Also these are associations which do not imply causality. In the lack of relevant trials, the statements made need to be reframed and supported (if data is available).

Response: We agree with the reviewers regarding these statements. We have reviewed the literature and added new references to this section. The studies that suggest a decline in CVD mortality are not population-based studies and there is limited data, especially from the U.S. in terms of mortality from CVD among patients with RA. Most recent studies still suggest increased mortality from CVD among RA patients compared to the non-RA population and even those that show a decline, it is still not to the point of the non-RA population. Below are the changes made to the manuscript.

“CVD is the leading cause of death even in the general population; however, RA augments the risk of developing CVD by almost two fold, a risk magnitude comparable to that of diabetes mellitus.[16, 17] Rheumatoid arthritis patients suffer from excess mortality from cardiovascular disease.[7, 18] RA patients are twice as likely to experience a silent myocardial infarction compared to non-RA subjects[4] and carry a higher burden of coronary plaques even in the absence of clinical history of coronary artery disease.[19] Following a new CVD event, patients with RA die with a 17.6% 30-day CVD mortality compared to 10.8% in the non-RA population.[20] These patients had an odds ratio (OR) and 95% confidence interval (CI) of 1.6, 1.2-2.2 for increased CVD mortality after 30-days of an myocardial infarction (MI) compared to the non-RA population.[20]

Similar findings were observed in a meta-analysis of 111,758 patients with 22,927 cardiovascular events that found a 50% increased risk of CVD death among patients with RA compared to the general population.[21] Another meta-analysis reported a 60% increase in CVD
death compared to non-RA subjects.[22] Results from Nurses’ health study found that women with RA had 45% increased CVD mortality with a hazard ratio (HR) of 1.45, 95% CI 1.14-1.83, compared to non-RA women.[18] Though the relative risk (RR) and rates of CV mortality may vary among different data sources owing to differences in patient population, duration of follow up, measurement of outcome and missing data on specific cause of death, these studies still considerably support the increase CVD mortality that exists among patients with RA.[23]

CVD mortality has been associated with level of inflammation, HLA–DRB1*0404[10], use of glucocorticoids[24] and presence of autoantibodies[25, 26], and can possibly be reduced by effective RA treatments.[27, 28] The time trend studies of overall mortality and CVD specific mortality in RA showed persistently increased CVD mortality except for some recent data suggesting a downward trend. A 2007 study by Gonzalez et al. demonstrated a widening gap between overall mortality in RA compared to general population.[29] A recent (2014) analysis from United Kingdom (U.K.) based cohort, Norfolk Arthritis Register, included 2,517 patients with early inflammatory arthritis with 16,485 person-years of follow-up. In this study, CVD mortality decreased with time in the first seven years from recruitment in this register, but was increased among patients who were antibody-positive.[25]

In a population-based incident RA cohort from Canada, Lacaille et al. reported improvement in overall mortality and a similar 5-year CV mortality in RA patients with disease onset in 2001-2006 to non-RA patients.[30] Another study showed improved CVD mortality in an RA cohort from 2000-07 (2.7%, 95% CI 0.6–4.9%) compared to patients diagnosed in 1990–99 (7.1%, 95% CI 3.9–10.1%) suggesting a decline in CVD mortality in more recent years.[31] It must be noted that results of this particular study were based on only 315 RA patients from a single county in the United States (U.S.) with 8 deaths from CVD, which could be a result of regional differences and may not represent the actual CVD mortality among patients with RA at a population level.[31]

Many of the studies that showed a decrease in CVD mortality in the U.S. were not population-based. In order to confirm an actual decrease in CVD mortality, larger population-based studies with longer follow up are needed. Overall, the data thus far remains robust in support of a current and persistent increased CVD mortality among patients with RA. [25, 32-36]”

Comment: Last paragraph. We cannot start sentences with "and".

Response: Text modified

HTN

Comment: Last sentence: I am not sure that epidemiological evidence emphasize causality.

Response: We agree with your comment that epidemiological evidence of hypertension in RA does not imply causality. In the second paragraph of the hypertension section, factors associated with HTN in RA are briefly mentioned, but they do not imply causation of HTN in RA by any means. We have modified the text to make sure that we imply, based on evidence, that these are associations and not causation.
“Prior studies report a wide range of prevalence of hypertension in patients with RA ranging between 3.8-73% in RA ranging between 3.8-73% [39-44]. Similar to the general population, hypertension is detrimental for CVD risk among patients with RA and is an independent predictor of CVD events. [41, 45] A meta-analysis of longitudinal studies, found 84% increased risk of myocardial infarction among patients with RA with hypertension compared to non-hypertensive patients with RA (relative risk (RR) 1.84, 95% CI 1.4-2.5).[46]

Multiple factors may impact blood pressure in patients with RA including inflammation, physical inactivity and drugs. [40] Increased arterial stiffness and reduced elasticity of blood vessels is seen in patients with RA. [47, 48] Several studies conducted in animal models suggested an association between ongoing inflammation and hypertension. [49] The exact underlying mechanisms remains to be fully understood. Interestingly, a study using data from the Women’s Health Study, an ongoing randomized, double-blind, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer, used women with incident hypertension. This study found that high C-reactive protein (CRP), was associated with increased risk of developing hypertension among healthy women. [50, 51] Finally, medications that are often prescribed to patients with RA, such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, have been associated with increased risk for HTN. [52, 53]

Obesity

Comment: It has been suggested that BMI cut-off points should also change in RA given that their body composition is significantly different to controls (higher adiposity and lower muscle mass).

Response: Thank you the comment. We have reviewed the literature and added the references that’s suggested BMI cut points in RA specific population as well as their value and limitations in explaining obesity-related comorbidity.

“A past study found that for a given body fat content, patients with RA had a significantly lower BMI, by almost 2 kg/m2 compared to general population. Investigators of this study proposed that BMI cut off for RA patients should be reduced to 23kg/m2 for overweight and 28kg/m2 for obesity respectively.[66] While it is an interesting observation, these cut off points have not been used extensively in population-based cohorts to determine whether these are more predictive of CVD events in patients with RA. Alternative measures that have been proposed include waist circumference and waist to hip ratio but thus far, they have not been proved superior to BMI in in assessing obesity-related comorbidity.[76] Further research is needed to identify the optimal way to define obesity in patients with RA.”

Comment: Lack of physical activity and exercise is a key aspect of managing CVD in RA (also highlighted in the recent EULAR guidelines). Why the authors have not discussed that at all, provided that increasing fitness and physical activity (these are different things) associates with improved CVD profile in RA?
Response: Thank you for the comment. We have addressed this in the manuscript. We have revisited the literature and added a new section on physical fitness and cardiopulmonary fitness. Please see the response to similar comment above.

Reviewer #2:

Comment: This is a narrative review of risk factors, cardiovascular risk assessment and treatment in RA. Since the literature is by now enormous in this field and continuously growing, a narrative review runs the risk of including some selection bias based on subsets of studies, e.g., availability or author selection. The present review is well written and informative and interesting to read. Generally, the references are adequate and actual, however far from comprehensive, and some of them are questionable. Although stated in the end of the Introduction, I think it is important to more clearly emphasize the narrative nature of the review, for example in a section on strengths and limitations. Such a chapter could shortly discuss the narrative review in comparison with systematic reviews and met analyses.

Response: Thank you for your valuable feedback. We have included the limitation of this manuscript being a narrative review. The added text appears as follow.

“As such, this narrative review does not address risk of bias of the articles included and it may not have taken into consideration all the available data as a systematic review would have done.”

Comment: Heading: State that this is a narrative review in the heading.

Response: We have changes the title of the manuscript to describe that this is a narrative review.

“Cardiovascular Co-morbidity in Patients with Rheumatoid Arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment”

Comment: Introduction: Page 3, line 44; Ref 8 must be wrong

Response: Thank you for pointing out. We agree that the reference was added by mistake. It has now been removed

Mortality/morbidity

Comment: Be careful to differ statements on mortality overall and CVD mortality. On page 4, I do not think Refs 12 and 13 on line 15, refer to CVD mortality but to overall mortality.

Response: Thank you for the comment. We agree with your statement. We have edited the section appropriately which is now focused only on the CVD mortality instead of overall mortality.
Comment: In the chapter on decreasing mortality, a recent publication from Holmqvist M and coworkers may be of interest (ARD 2017, doi: 10.1136/annrheumdis-2017-212131)

Response: Thank you for the interesting paper. We have included the reference in our updated manuscript.

Comment: The paragraph that starts on page 4, line 51, is somewhat hard to follow, e.g., "50 % increase of CVD death" is followed by "increased risk of CVD by almost 2 folds" (page 5, lines 4-23). Please clarify the difference between statements regarding cardiovascular morbidity and mortality, respectively

Response: We have modified the text to make it clearer. The updated manuscript shows new references added for CVD mortality only.

Traditional Cardiovascular Risk Factor

Comment: In this paragraph, it is somewhat hard to know which statements on association between hypertension and inflammation concern general population and RA respectively. For example - line 39 refers to RA as does line 47, but what about lines 42-44 which concern inflammation and hypertension?

Response: Thank you to the reviewer for pointing out this. We agree that it needs rephrasing for clarity. We have modified the entire hypertension section for that same reason. We have divided this section into: 1. Prevalence of HTN among patients with RA; 2. Association of inflammation with HTN in the general population. The point for this section is that even though this association has not been determined among patients with RA, the fact that has been observed in studies of healthy women, suggest that inflammation (as frequently occurs in RA) can be another factor associated with HTN and as a consequence CVD. See the paragraph below; 3. Gap in treatment of HTN among patients with RA; 4. Consequences of uncontrolled HTN in RA from the CVD perspective.

“Multiple factors may impact blood pressure in patients with RA including inflammation, physical inactivity and drugs. [40] Increased arterial stiffness and reduced elasticity of blood vessels is seen in patients with RA. [47, 48] Several studies conducted in animal models suggested an association between ongoing inflammation and hypertension. [49] The exact underlying mechanisms remains to be fully understood. Interestingly, a study using data from the Women’s Health Study, an ongoing randomized, double-blind, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer, used women with incident hypertension. This study found that high C-reactive protein (CRP), was associated with increased risk of developing hypertension among healthy women. [50, 51] Finally, medications that are often prescribed to patients with RA, such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, have been associated with increased risk for HTN. [52, 53]”

Comment: Please state also that the initial sentences regarding Insulin resistance/meabolic syndrome refer to the general population.
Response: We added general population to the statement for clarity.

Smoking

Comment: Page 8: Again, I do not think that Refs 12-13 refer to CVD and CVD mortality but to mortality overall. Further, although there is now some support for smoking being a risk factor for CVD in RA, several large studies could not verify this. I think authors should be careful with their conclusions.

Response: We agree that some studies in the past did not show a strong association of smoking with CVD. We have cited and discussed those studies. We have also included more recent studies and meta-analysis that do show the impact of smoking on CVD risk in patients with RA.

The references for overall mortality have now been omitted. The updated text highlights CVD mortality in patients with RA and smoking effect on CVD risk in this population.

The modified text is as follows.

“Patients with RA who smoke have aggressive disease and worse clinical outcomes.[77] Despite the associated hazards, the prevalence of smoking is higher in patients with RA compared with controls (OR 1.56, 95%CI 1.35-1.80).[78] In the general population, cigarette smoking is associated with CVD.[79] Although among patients with RA its impact on CVD is less clear, some studies in the past showed that there was a weak association between smoking and CVD in patients with RA.[5],[80] However, it is possible that this weak association is attributed to under-reporting of smoking status[81] or index event bias (a type of selection bias that occurs when multiple risk factors contribute to the risk of the index outcome (disease) as well as disease sequela).[82]

It is known that cigarette smoking is associated with rheumatoid factor positivity [83], production of anti-citrullinated antibodies (CCP) [84], increased disease severity[77], and poor response to treatment[85], all of which have been associated with CVD morbidity in patients with RA.[25, 26, 86, 87] More recent data have shown that smoking is associated with CVD risk. In a large longitudinal study from the Veterans Health Administration (VHA), (37,568 patients with RA and 896 incident hospitalized myocardial infarction) “current smoking” was associated with an increased risk of myocardial infarction by 42% vs. “never smoker” (HR 1.4, 95% CI 1.1-1.8).[88] Another study of 5,638 patients with RA with no prior CVD who were followed for 5.8 years found that smoking had the highest population attributable risk (PAR) for CVD across different CVD risk factors including RA disease activity (PAR for smoking = 23.7%).[89] Moreover, a recent meta-analysis of longitudinal studies noted a 50% increased risk of CVD events in smokers compared to non-smoker RA patients (n=2,056, RR 1.5, 95% CI 1.25-1.8).[46] A significant number of patients with RA continue to smoke therefore, interventions for smoking cessation should be applied not only to improve RA disease activity but also to ameliorate their overall CVD risk.”
RA related factors

Comment: Page 11, last lines: In the association between CRP and atherogenesis really determined? The references are rather old and I think this is still rather a hypothesis. I suggest that the authors to be more careful in this statement.

Response: Thank you for the comment. We have revisited the literature and modified the text discussion to reflect available evidence of different RA related factors in atherosclerosis. We have included the reference of association of CRP with intima thickness, which is a surrogate for atherosclerotic disease. The modified text appears as follows.

“Atherosclerosis is no longer thought to be a simple process of lipid accumulation in blood vessels. There is evidence that systemic inflammation plays a pathogenic role in the development of accelerated atherosclerosis. Atherosclerotic plaque formation begins with endothelial dysfunction, after which pro-inflammatory cytokines and adhesion molecules are released. Inflammatory cells then enter the blood vessel wall along with LDL molecules because of increased endothelial permeability. LDL is oxidized and taken up by the macrophages, which later become foam cells. This is followed by smooth cell proliferation and neovascularization which ultimately cause the thickening of the blood vessel and plaque formation. [12] Regardless of the source of inflammation, a study found that elevated inflammatory markers were associated with increased CVD risk in healthy men. [127]

Past studies have shown that endothelial dysfunction was impaired in RA patients [127] with a magnitude equivalent to that of diabetes, an independent CVD risk factor.[17] Circulating inflammatory substances and autoantibodies, such as anti-CCP and rheumatoid factor, are associated with endothelial dysfunction.[128, 129] A recent systematic review of randomized clinical trials suggested that endothelial dysfunction in RA can be improved with TNF alpha-blockers, but the conclusion was based on small observational studies and further randomized controlled data is needed to validate these findings.[130] Similarly, inflammatory cytokines such as IL-6, IL-18, and TNF-α, which are typically elevated in rheumatoid arthritis, have been associated with coronary artery disease.[131] Markers of inflammation in patients with RA such as ESR and CRP are associated with intimal media thickness, a surrogate for atherosclerotic disease.[132-134] There is also development of pro-atherogenic HDL in the setting of inflammation from RA.[135, 136] Inflammation thus significantly contributes to CVD risk in patients with RA in addition to traditional CVD risk factors.”

Cardiovascular risk assessment

Comment: Maybe Reynold’s risk score" should be mentioned here, since it takes inflammation as measured by CRP into account.

Response: Thank you for the suggestion. We have included the reference on Reynold’s risk score. The modified text is as follows.
“The Reynolds risk score was developed from prospective cohorts of men and women without diabetes.[146, 147] It does account high sensitivity CRP into the equation, so theoretically it can better predict CVD risk in RA. However, CRP is more sensitive for short-term changes in inflammation. A clinical study found that, despite accounting for CRP, the Reynolds risk score substantially underestimated CVD risk in patients with RA (both men and women).”

Management.

Comment: Page 17 line 9. There are several studies showing the predictive effect of IMT so I miss a reference to the statement on limited predictability.

Response: We reviewed the literature again and we found that the limited predictability of IMT is for the general population in which CT scan and carotid calcifications are more predictive of CVD than IMT. However, in patients with RA there are several studies that still support that IMT does predict CVD in this population. Hence we have deleted the statement regarding limited predictability from IMT in patients with RA.

Comment: Page 17 line 43. I suggest "Traditional risk factors and role of RA therapy" in analogy with a.

Response: We were not very clear in regarding this comment from the reviewer. We would like to bring up that the main point of this paragraph was that regardless of disease activity, medication used to treat RA, may provide have an intrinsic benefit in decreasing CVD risk.

“Del Rincón et. al. demonstrated that even in the presence of high level of inflammation (represented by ESR), anti-TNF therapy and MTX decrease the progression of intima-media thickness (IMT). [133]”

Comment: Page 17 last line and first on page 18: The effects of NSAIDs and glucocorticoids on cardiovascular risk factors are diverse and should be discussed more extensively. The effect of corticosteroids on cardiovascular risk overall may also be beneficial since they lower inflammation. The overall impact is hard to control for because of "confounding by indication". I miss several references in this area. At least, this issue has to be discussed more extensively by the authors.

Response: We thank you for your suggestion. We have added a new paragraph of evidence of NSAIDs and glucocorticoids. The modified text appears as follows.

NSAIDs and Glucocorticoids(GCs):

“A broad use of NSAIDs and GCs is common among RA patients by virtue of their anti-inflammatory properties. However, these drugs have implications pertaining to CVD risk. GCs are associated with insulin resistance[55], hypertension[56], obesity, hyperlipidemia[57] and diabetes mellitus[58], all of which are associated with development of CVD. They are associated
with CVD mortality in a dose dependant fashion.[39] On the contrary there are some other studies that suggested that GCs may prove beneficial in reducing CVD risk by controlling inflammation.[59] Robust randomized data to prove this notion is lacking and EULAR currently recommends keeping GCs at a minimum dosage.

NSAIDs have been associated with CVD risk in the general population, but whether they augment CVD risk in RA needs to be well established. A systematic review and meta-analysis showed that NSAIDs increase risk of CVD events in RA.[138] However, the effect was mainly driven by rofecoxib and not from non-selective NSAIDs or celecoxib, another COX2 inhibitor. Rofecoxib has now been withdrawn from the market and the recent PRECISION trial found similar CVD safety of celecoxib to ibuprofen and naproksen in patients with arthritis (~10% of total population had RA).[139] In the Danish cohort, investigators found a significantly lower CVD risk associated with NSAIDs in RA compared to non-RA.[140] The evidence as of yet is not strong enough to contraindicate the use of NSAIDs in patients with RA and the recommendation is to use them cautiously in this population.[13] A meta-analysis found naproksen to be least harmful for CVD safety.[141] Nevertheless, further research is needed to understand the impact of NSAIDs in RA patients, particularly in patients with pre-existing CVD risk factors.”

Comment: Page 19, lines 27-29. As pointed out above, the statement on a decreasing trend of CVD event in RA has weak evidence. I lack references to the statement. Refs 16 and 17 concern trend of overall mortality in patients with RA which should be clarified in the sentence on line 32. Although plausible that this refers to all underlying causes, I suggest a more careful conclusion.

Response: Thank you for this comment. We have addressed this in the mortality section above. Also the first 5 lines of second last paragraph have been deleted.

Comment: Page 19, last paragraph: I agree with the authors in their recommendations to assess and manage all modifiable cardiovascular risk factors and to control disease activity in patients with RA. However, the emphasis on statin treatment is based on 10-year prediction model from ACC/AHA is valid in USA which has to be stressed. The EULAR recommendations (ref 7) recommend treatment according to SCORE or to prediction models used locally and do not emphasize statin treatment in the last update. This has to be better clarified with due references.

Response: Thank you for your comment. We agree that ACC/AHA is valid only in US. We have modified the text as below

“According to the ACC/AHA cholesterol treatment guidelines, statins should be initiated for primary prevention if the calculated 10-year CVD risk ≥ 7.5% for patients between 40-75 years of age in the U.S. [146] Once a CVD event has occurred (secondary prevention), every patient with RA should be initiated on a statin. In other countries (such as European countries), statin initiation can be carried out per national guidelines of CVD management for general population. [13].”
Comment: The language is generally good, but there are several misspellings and other typographic errors, e.g.,

Page 3, line 15: "…risk factors and…" what?

Page 7, line 2: "patient´s" ??

Page 7 line 54: " obesity exerts …"

Page 8 line 3: delete "is" page 10, line 51 "..with s pattern"

Page 11 line 48 "…in RA patients"

Page 12, line 35 "…diseases have been…”

Page 15, line 20 "…is more?? associated…”

Page 17, lines 12, 15, 23… and on page 18, lines 51-59 there are several small errors. Please look over!

I miss a comma between risk factors and cardiovascular risk.

Response: Thank you for a thorough review of the paper. We have reviewed the manuscript and have it edited by a language editor.