Author’s response to reviews

Title: Methotrexate therapy impacts on red cell distribution width and its predictive value for cardiovascular events in patients with rheumatoid arthritis

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To the Editors of BMC RHEUMATOLOGY

Dear Dr. Javier Rodríguez-Carro!

Please find enclosed a carefully revised version of our manuscript entitled, “Methotrexate therapy impacts on red cell distribution width and its predictive value for cardiovascular events
in patients with rheumatoid arthritis (BRHM-D-17-00036R1)" which we want to re-submit as an original article to BMC- Rheumatology.

We were happy about the positive evaluation of our manuscript and your encouraging comments. We were also grateful for the suggestions of the reviewers which we addressed in the revised version of our manuscript, as outlined in our point to point reply.

None of the authors has any financial disclosures or conflicts of interest in relation to this study.

We hope that you will find our manuscript will be now acceptable for publication in BMC rheumatology and we are looking forward to receive your editorial decision.

Sincerely,

Günter Weiss, MD
Corresponding author

POINT TO POINT REPLY

Technical Comments:

Editor Comments:

The authors have taken into account the points raised by the reviewers. In some cases, the comments were included as limitations of the study. Overall, the manuscript has improved.

However, the manuscript contains some format mistakes that must be clarified to avoid potential misunderstanding. In page 6 (line 8 and line 58) and page 7 (line 77) -pdf file-, some error messages appear as ("Error! Reference source not found!"). These messages may be caused by a erroneous cross-reference to manuscript tables (tables 1, 2 and 3, respectively). However, this issue must be clarified by the authors before guiding this manuscript forward in the peer review process.

The problems you mentioned may have been due to the fact that the tables were inserted in hyperlink format. We have corrected that issues and these problem has been solved. (page 6 (line 8 and line 58) and page 7 (line 77))
Reviewer reports:

Miguel Ángel González-Gay (Reviewer 1): This study indicates that red cell distribution width (RDW) may be a marker of future cardiovascular events in patients with rheumatoid arthritis (RA) not taking methotrexate (MTX). It is already known that MTX Methotrexate inhibits dihydrofolate reductase, which leads to accumulation of polyglutamated folates. Consequently RDW may be increased in patients taking this synthetic DMARD. Nevertheless, several studies indicate that MTX use is associated with reduction in the mortality of patients with RA, mainly due to a reduction in the cardiovascular mortality. Therefore, it is possible that the anti-inflammatory effect mediated by MTX may compensate the potential negative effect derived from its anti-folic action.

The authors confirmed the expected association of cardiovascular events and age/disease duration.

This study is of potential interest. I do not have major points of criticism. Potential limitations have been elegantly discussed by the authors. Methods are sound. Results are presented clearly. However, I have a few comments/suggestions that from my point of view may improve the Discussion:

1) Page 11: Lines 19-21: Highlight the potential relevance of "the genetic component" in the risk of cardiovascular disease associated to RA as follows:

Therapy and CV events with other important variables including classic cardiovascular risk factors, "the genetic component" or iron homeostasis. [3, 31, and a new Ref. 32]


2) Page 11-Line 21: Also, add the following paragraph along with the corresponding references:

"In this regard, patients with RA who carried the methylene tetrahydrofolate reductase (MTHFR) 1298 allele C frequency were found to have an increased frequency of cardiovascular events after 5 years and 10 years of follow-up. Moreover, patients carrying the MTHFR 1298 AC and CC genotypes had a significantly decreased flow-mediated endothelium-dependent vasodilatation (a marker of endothelial dysfunction that is an early step in the atherogenesis process) when compared with those carrying the MTHFR 1298 AA genotype [new Ref. 33].
More recent results also indicate that MTHFR expression is significantly reduced in patients with RA compared to controls [new Ref. 34]. It was found especially true for RA patients with ischemic heart disease [new Ref. 34]. Taken these considerations together, these results indicate that MTHFR gene may influence the risk of subclinical atherosclerosis and cardiovascular disease in patients with RA."


We thank this reviewer for the positive comments regarding the quality and significance of our study. We appreciate the valuable suggestion to mention the role of MTHFR in RA and its linkage to cardiovascular risk. We added the two statements along with the corresponding references.

Giuseppe Mandraffino (Reviewer 2): Manuscript Number: BRHM-D-17-00036_R1

Review file for Editor and Authors

Title: Methotrexate therapy impacts on red cell distribution width and its predictive value for cardiovascular events in patients with rheumatoid arthritis

In this paper, Julia Held and coll aimed to evaluate whether MTX treatment may impact on RDW also as predictive factor for CV invents in RA patients.

They analyzed the data from 385 outpatients, on different drug regimens, and concluded that MTX affects RDW but it makes difficult to use this parameter as prognostic index.

This referee has several issues to be addressed:

First, the paper is poorly written; the authors should significantly improve their manuscript, including spacing and punctuation. Also, according to the journal style, they should state if reference have to be showed before or after the full stop, consistently.
We have carefully written this paper and it was now finally checked by a native English speaker. We apologize for typing and grammatical errors which have been corrected in the revised version of the manuscript.

Second, the paper is a bit too puzzled; several paragraphs need to be re-organized, also avoiding repetitions.

It was not clear to us which paragraphs were exactly meant. We tried to give a good introduction of the topic and its relevance for RA and we presented our results according to the stepwise process of our investigations. Our presentation was well appreciated also by reviewer 1 who made the statement that our “results are presented clearly”. We re-structured some sentences and hope that this will fulfill the reviewers expectations.

Third, please check for every abbreviation; the authors well know that they have to extensively write the first time, then using the abbreviation.

Thank you for this suggestion, we checked all abbreviations and performed the necessary modifications.

Fourth, an issue about the statistic strategy; considering the vey low rate of CV events (6%), had they performed a power analysis before the data exploiting? Considering the whole studied population (385 pts), about 2/3 out of them were assuming MTX, and the same percentage of patients on treatment experimented a CV event.

This was a retrospective analysis of a patients’ cohort with the aim to study the influence of co-
mediations of RA patients towards the predictive value of RDW for severe cardiovascular events. We agree with the reviewer that the rate of events was considerably low, however, this were the real life data of our patients. As mentioned in the discussion and in agreement with the suggestion of the reviewer it will be thus of interest to verify the observations of our pilot study in big consortia with higher patient and event numbers.

Moreover, it is unclear whether different drugs were prescribed top different clinical subsets of patients (this is an unavoidable bias of retrospective studies); different patient subsets may have different CV risk at baseline. Also, it is unclear how CCS use is distributed in the study population, and its impact on CV prognosis.
The co-mediations of patients, specifically in regard to immuno-suppressive therapy, were evaluated and their impact on cardiovascular events and RDW were statistically analyzed and are presented in Table 2 and Table 3.

Fifth, it seems that baseline CV risk (including the prevalence of known CV risk factors: arterial hypertension, dyslipidemia, diabetes mellitus, smoking habit, family history, ...) of enrolled patients has not been evaluated, as well as the co-administration of drugs potentially able to modify CV outcome (statins, beta-blockers, ASA, RAAS inhibitors, ...).

We thank the reviewer for this comment. A more accurate evaluation of cardiovascular risk factors in patients with RA from the beginning would be desirable given the important role of cardiovascular events for morbidity and mortality of RA patients. However, in this retrospective analysis these data were not available. We thus included a statement in the discussion pointing to this specific limitation of our study.

The authors should clearly explain how they managed the potential confounders, and the actual strength of their statistic strategy (event rate seems to be too low, and too low more when you are considering the combination of event rate with so many regimens).

We performed a regression analysis including several co-founders. The results of multiple logistic regression and binary regression analysis are shown in Table 5 evaluating the effects of co-founders toward RDW. Because severe cardio-vascular events were not so frequent we could not perform a meaningful regression calculation analysing the relative contribution of several co-founders for cardio-vascular events which was also not the primary aim of this study.

Last, please thoroughly check for why you lost so many in-text references: (Error! Reference source not found.).

In our hands all references are clearly indicated. I am afraid that this inconvenience for the reviewer may have arose from software incompatibilities which did not occur with reviewer 1 or the editor. We hope that the revised version of our manuscript does not show this problem anymore.

At this point of the academic revision, I cannot go further without the authors address these main points.