Reviewer's report

Title: The association between C-reactive protein and the likelihood of progression to joint replacement in people with rheumatoid arthritis

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Reviewer: Andrew P Andonopoulos

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The present study has examined the association between CRP and the likelihood of joint arthroplasty in RA patients. Although it has long been known that high CRP levels, along with certain other parameters, represent a poor prognostic factor in RA, necessitating the introduction of early aggressive treatment, still the present study offers information of some significance, because it correlates high CRP levels, and even more their fluctuation over time, with a specific end point which is total joint replacement.

Probably, a major shortcome of the study is its retrospective character and another one is its cohort, which originates from a dataset of general practice and not of a rheumatology practice. The latter might have affected the type of care the patients had been receiving, with regard to treatment and regular clinical and laboratory evaluation (including CRP measurements).

Below are several points of significance, which the authors should pay special attention to.

Abstract

The way they are written, the terms acute and sub-acute appear as if referred to CRP status. This is not correct. These terms apply to clinical conditions and not to laboratory values. They should therefore be used as indicative of acute or subacute disease status.

Furthermore, the arbitrary cutoff at the level of 10mg/L of CRP, to indicate acute or sub-acute disease, is rather inappropriate. This is more important especially for values just or slightly above 10mg/L, which may not reflect significant disease activity, as values well above this level would. This point, to our opinion, is particularly important, and we would suggest that the authors use wider ranges of CRP values to categorize disease activity (**).

In lines 11-12, the way it is written the phrase suggests that the analysis was associated with a 36% increase in the hazard ratio of surgery. It should be corrected to indicate that the increase (itself) in log mean CRP is associated with the risk.

In line 14, “Repeated CRP observations around one year apart”: Does this mean that CRP values were recorded once a year? If yes, this does not accurately reflect the disease activity status of the patients during the observation periods. They should have had more than one CRP determinations per year (**).
Introduction
The studies referenced by the authors #2, 3 and 4 have been published prior to the introduction of anti-TNF treatments, therefore they do not reflect the current status of the long term prognosis of RA. The same may be true for reference #1. No one of the patients in that study had received biologics (**).

In page 4, lines 1-2: ESR and CRP are not biochemical parameters.

Line 7 of the same page: Reference #12 does not refer to orthopedic prognosis in RA but to cardiovascular prognosis in dialysis patients. Therefore the authors, just before citing that reference and at the end of the sentence, should write: “as has been true for evaluation of the effect of such changes upon the risk of cardiovascular disease in other patient groups (12).”

Patients and methods
Page 5, five lines from bottom: Instead of “Data from THIN of four categories…..” write “Data from THIN consist of four categories…..”

Page 6, line 2: Write “of” instead of “for”.

Line 4: “at least” should be replaced by “less than”

Line 6: “composite” is not appropriate, because the index event is the first (i.e. one) of three events

Line 8: Write “consecutive” instead of “concurrent”

Line 12: “index date” should be defined. It apparently refers to the index event

Line 13: Comma should be placed after “presentation”. By the way, but very importantly, commas should be added at several points in the text, because their absence in the current version, may make understanding difficult (**).

The authors are using the terms index event, index date and observational index, without defining them accurately. They should do that.

Page 7, Line 2: “biochemical” should be omitted

Line 3: Add “value” following 0

Line 4: “if” should be replaced by “that”

Line 9: Write “CPHM” instead of “CHPM”

The second paragraph fits better to the Results section

Third paragraph: The authors say that they included CRP changes “where at least two observations were recorded approximately one year apart (±90 days in order to recruit sufficient cases)”. This statement may imply that the majority of their cases had hardly two CRP observations within 9-15 months, which, if true, is rather inappropriate in the follow up of a chronic inflammatory disease such as RA. Furthermore, the mean values obtained from these CRP observations may not be reflecting the CRP evolution over the observation period. Following that, the authors claim that the baseline CRP values and those of follow up were defined as the average or mean of the values obtained within 90 days of the observation. They should provide some information about the average number of CRP determinations over the observation periods (**).
Page 8, Line 1: Write “process” instead of “processes”

Line 3: Add an “a” between “in” and “recent”

Statistical methods: They refer to Survival only. But is survival the major end point of the study???. (**)

Results.

Page 9, First Paragraph: It is very unclear how many CRP determinations in average corresponded to each case subjected to joint replacement. If the 24,023 CRP observations corresponded to the 125 cases with joint arthroplasty (which was performed after an average of 49 months following diagnosis of RA), this roughly would suggest that each such case had an average of 4 CRP measurements per month. Is that true???. If yes, it should be stated. If not, then the authors should better provide more accurate data and in a more understandable way (**).

Also, the fact that “Among 7,121 cases with newly diagnosed rheumatoid arthritis, 3,576 had at least one valid CRP measurement…..” indicates that the remaining 3,545 did not have any CRP determination. Is that true???. If yes, this indicates a poor follow up practice of the RA cohort studied (**).

Second Paragraph: “have”’s should be replaced by “had”’s.

Page 10, 2nd paragraph: It is stated that “Repeated CRP observations at one year were available for 1,287 subjects, of whom 54 experienced at least one major joint replacement”. It is unclear whether these figures ascertain statistical significance to the results. This is extremely important, because it is this cohort of 1287 individuals (of whom 54 ended up with arthroplasty) which provides “novel and meaningful” information to the study, i.e. the effect of CRP evolution upon the end point of joint replacement. Perhaps the authors should focus on this group only, because the data on the remaining, with only one CRP determination, offer nothing new, since they represent crossectional study results. (**)

3rd Paragraph: The authors should change the sentence, because what they really mean is that: the hazard of TJR in the preexisting acute (AA) cases was twice that of stable sub-acute (SS) cases.

Tables 1 and 2 should be supplemented with legends, explaining the abbreviations used (**).

Finally, in the discussion section, the authors should be somewhat less adamant about the “striking” correlation of mean CRP change with TJR outcome, keeping in mind the limitations of their study (**).

In conclusion, the manuscript should undergo extensive revision, before its appropriateness for publication is decided. Especially, the (**)s and (**), where appear in this report, indicate points of major significance, which the authors should pay attention to and clarify them the best possible way (major compulsory revisions).

Level of interest: An article whose findings are important to those with closely
related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests