Author’s response to reviews

Title: Association between adherence to statin medications and likelihood of cardiovascular events among US managed care enrollees

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Author’s response to reviews: see over
Dear Editor:

Please see below our responses to the reviewers’ comments, to accompany our revised manuscript. Thank you for the opportunity to revise and resubmit this paper.

Regards,
Rick Chapman

1st Reviewer's report

Title: Association between adherence to statin medications and likelihood of cardiovascular events among US managed care enrollees

Version: 1 Date: 12 January 2010

Reviewer: Diana Brixner

Reviewer’s report:
- Major Compulsory Revisions

MY CONCERN HERE IS THAT THE TITLE DOES NOT MATCH THE WORK DONE, I READ THE WORK AS A COMPARISON OF COMBINED STATIN AND CCB VS TAKING THESE AGENTS TOGETHER AS A SINGLE PILL OR AS SEPARATE AGENTS. THE TITLE ONLY MENTIONS STATINS, AND THAT IS NOT THE WORK THAT WAS DONE, NEED TO INCLUDE THE CCB, HYPERTENSION TREATMENT COMPONENT.

We have changed the title to read “Association between adherence to calcium-channel blocker and statin medications and likelihood of cardiovascular events among US managed care enrollees”.

THE ABSTRACT IS NOT COMPLETE, DO NOT START OFF THE METHODS OF ABSTRACT IN THE FIRST PERSON.

We have changed the first sentence in the Abstract methods section from “We conducted a retrospective cohort study…” to “A retrospective cohort study was conducted….”

THE INDEX SHOULD BE DEFINED IN THE ABSTRACT, ESSENTIALLY IT IS PART OF THE FIRST SENTENCE.
We have added text to the first sentence of the Abstract methods, clarifying that this is the index event

NEED TO INCLUDE THE RATE OF CV EVENTS, IE WITHIN ONE YEAR POST INDEX DATE?

We have clarified that we examined “the rate of CV events from 6 to 18 months following index date”.

LEVEL THREE IS NOT EASILY UNDERSTOOD AS TO WHAT THE PURPOSE WAS OF STUDYING THOSE COHORTS. IS IT TO SHOW THAT EVEN IF YOU ADD NON ADHERENT PATIENTS ON THE COMBINED THERAPY TO THE ADHERENT GROUP, OVERALL THAT GROUP WILL STILL HAVE LESS EVENTS THAN THOSE WHO ARE NON ADHERENT ON DUAL THERAPY? THIS TO MEANS SEEMS TO BE A CONTRIVED COHORT THAT IS MORE ABOUT MARKETING A COMBINED PILL THAN TRUE SCIENCE. THE WORK STANDS ALONE WELL WITH JUST THE 1) AND 2) COHORTS AND COMPARISONS AND I WOULD SUGGEST DELETING 3) AND PROVIDING MORE DETAIL AND COMPARISON AMONG 1) AND 2). THE POINT OF THIS WORK IS THAT ADHERENCE IS COMPAReD ALONG WITH THE RATE OF CV EVENTS, WHICH FOR THE MOST PART HAS NOT BEEN DONE BEFORE, THAT IS WHAT THE MAJOR CONTRIBUTION IS OF THIS WORK, THE COMPARISON OF 3) DETRACTS FROM THIS. THE CONCLUSION IN THE ABSTRACT SUMMARIZES THIS WELL.

The first model includes adherence but not cohort, the second includes cohort but not adherence. The third model is constructed to understand the relationship between treatment-related differences observed in model 1 to adherence differences observed elsewhere in the paper. Since cohort and adherence are correlated, simply putting both factors, adherence and cohort, in a single model creates an interaction that splits the impact over each factor. The 4 cohort model is the application of an interaction term, cohort*adherence, that allows the model to behave properly given this relationship. Level three also shows consistency in benefit of adherence regardless of the form the product is administered, as would be expected. Given that part of the analysis demonstrates differential adherence by single vs dual pill administration, it is logical to consider whether the relationship with adherence and outcome is consistent by form.

Upon review of the paper, however, it did appear that the impact of non-adherent SPAA therapy on CV events may have been overstated, as the outcomes in this cohort were not significantly different from non-adherent CCB/Statin therapy. We have clarified the results in the main paper and abstract to note that the adherent cohorts were each significantly different from the larger non-adherent cohort (CCB/Statin).
PLEASE DESCRIBE WHAT CV EVENTS WERE LOOKED AT IN THE ABSTRACT.

We have added a list of the CV event types to the Abstract methods section.

THE PATIENT IDENTIFICATION RESULTS WOULD BENEFIT BY A FIGURE THAT DEMONSTRATE THE PATH OF EXCLUSION IN THE PATIENT DATABASE, HOW YOU GET FROM THE 65 MILLION PATIENT BASE TO THE STUDY COHORT. HOW MANY HAD THE HPTN DIAGNOSIS THAT WAS REQUIRED, THEN HOW MANY OF THOSE ON CCB AND STATIN ALONE, AND THEN HOW MANY WHERE THE OTHER WAS ADDED, ETC. THERE IS MUCH INTERESTING DATA TO BE GLEANED FROM DESCRIBING THIS PATHWAY AND IT WOULD PROVIDE THE READER WITH A GREATER COMFORT LEVEL IN UNDERSTANDING THE PATIENTS COHORTS (AGAIN THIS IS PART OF THE RECOMMENDED TRADE OFF VS. PATIENT COHORT 3).

We agree that this information would be helpful for the reader, and have added a Figure 2 detailing the number of patients disqualified by each of our exclusion criteria.

- Minor Essential Revisions

PAGE 5 FIRST LINE MAIN PARAGRAPH WHAT IS THE TYPE OF EVIDENCE THAT HAS LINKED POOR ADHERENCE TO CV EVENTS, IS IT FROM CLINICAL TRIALS? OTHER? RELEVANCE OF MEASURING THIS IN A CLAIMS DATABASE VS. OTHER METHODS? THE DATA PRESENTED ONLY SUPPORTS THIS ASSOCIATION WITH STATINS, WOULDN'T IT BE THE SAME ALSO FOR HYPERTENSION? REFERENCE TO PREVIOUS WORK IN THIS AREA SHOULD ALSO BE INCLUDED.

We have clarified in the text that the studies we discuss here are retrospective analyses, and so only demonstrate an association between higher adherence and lower CV event rates. We have also added references supporting the association between antihypertensive therapy and CV events.

IN METHODS A GREATER DISCUSSION AS TO WHY PDC WAS CHOSEN VS. OTHER ADHERENCE MEASURES, ALSO REFERENCE THE PDC METHOD

We have added text to the Methods section justifying our use of the PDC measure, as well as references for the measure and its use in the adherence literature.

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

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
2nd Reviewer's report

Title: Association between adherence to statin medications and likelihood of cardiovascular events among US managed care enrollees

Version: 1 Date: 26 January 2010

Reviewer: Holly Batal

Reviewer's report:
This was a very interesting article with important conclusions. I believe that the study was well done and well written.

- Major Compulsory Revisions
The wording of the last sentence of the results section of the abstract is confusing and should be clarified so that the points being made are crystal clear.

We have re-worded this sentence to attempt to clarify our meaning.

In the methods and results the factors that were controlled for in multivariate analysis should be listed out

We have listed the independent variables in the multivariable analyses in “Statistical analyses” under the Methods section, and have referred to that list in the Results section.

- Minor Essential Revisions
The label for reference 26 is duplicated

The reference list has been revised.

I found table 2 confusing. I think that the mean, sd, and median and what they represent are not clear and should be clarified.

We have changed the row headings in this table, to clarify what is being shown here (N and % of patients with PDC >=80%, as well as mean, SD, and median of PDC).

Weird last page with a partial title page

We are not sure what this refers to, but assume that it was an artifact created when the document was converted to PDF format.

- Discretionary Revisions

I would like clarity in the methods of how CV events that occurred in the 6 month
adherence period were dealt with.

*We have added a sentence to “Study outcomes” in the Methods section, clarifying that: “Any CV events that may have occurred in the first 180 days post-index were ignored for the purpose of this analysis.” We did not feel that such early events could be assumed to be related to adherence levels of the index medication that had only recently been initiated."

In the study outcomes section the paragraph “Secondary prevention patients were excluded…” belongs in the study population section of the

*We have moved this paragraph into the “Study population” subsection.*

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests'