Reviewer's report

Title: Comparing marginal structural models to standard methods for estimating treatment effects of antihypertensive combination therapy

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Reviewer: Evan Thacker

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This article by Tobias Gerhard and colleagues addresses an important issue in hypertension treatment research, namely how to validly estimate the effects of different antihypertensive treatment regimens on cardiovascular outcomes, controlling for confounding by time-varying blood pressure levels, in an observational (nonrandomized) setting.

This article will be a very nice contribution to the literature in terms of illustrating the use of the marginal structural Cox model, and in terms of its substantive finding – that with the use of appropriate statistical methods, more aggressive antihypertensive treatment was found to be associated with lower risk of a composite outcome of myocardial infarction, stroke, or cardiovascular death. This article could also be useful as a practical example in an epidemiologic methods teaching setting.

Major compulsory revisions

1. Could the authors separately address the issues of (a) time-dependent confounding and (b) differential loss-to-follow-up? In its current form, the analysis lumps these two issues together by comparing the standard Cox model with the marginal structural model that accounts for both issues simultaneously. As a consequence, the authors are somewhat limited in concluding that the bias in the standard Cox model is due to either time-dependent confounding, or differential loss-to-follow-up, or both (see Discussion paragraph 1 and Discussion paragraph 14). I feel that the paper could be considerably strengthened by isolating these two issues and commenting on the relative effects of each. Perhaps this could be accomplished by including a marginal structural Cox model that accounts for time-dependent confounding via IPTW but does not account for differential loss-to-follow-up, as well as a model that accounts for differential loss-to-follow-up via IPCW but does not account for time-dependent confounding.

Minor essential revisions

2. Introduction paragraph 4: For clarity, consider adding a phrase to this sentence: “However, if L is controlled in the analysis THROUGH CONVENTIONAL STATISTICAL METHODS, then L1, …”

3. Introduction paragraph 5: The first sentence mentions previous work in arthritis and HIV, but also cites an article about cardiovascular mortality (reference 9)
along with the references for arthritis (reference 8) and HIV (reference 10). Either cardiovascular mortality could be added to the list of previous work, or reference 9 could be dropped.

4. Using the term “SBP control variable” to refer to aggressive vs. conventional treatment seems confusing (Methods paragraphs 8 & 9), maybe because the models also included “SBP” variables or because the paper refers to prior work in which blood pressure control itself was the outcome of interest. I suggest replacing the term “SBP control variable” with “antihypertensive treatment variable.”

5. Please check the reference formatting – several did not list the year of publication, including refs 2, 3, 5, and 6.

Discretionary revisions

6. Abstract: The Conclusions section restated the results but did not give any interpretation. Consider mentioning something about the importance of using appropriate methods to deal with time-dependent confounding and differential loss-to-follow-up, or stating some other implication of the findings.

7. Throughout the paper, consider whether the description of MSM estimates as “unbiased” is too strong – could it be more appropriate to claim that they are “less biased” than conventional estimates?

8. Figure 1 and corresponding text in Introduction paragraph 4: Consider revising the figure and text to refer explicitly to “Blood pressure,” “Aggressive treatment,” and “CHD outcome” instead of “Confounder L,” Treatment A,” and “Outcome Y.” This revision could make the figure more concretely connected to the rest of the paper.

9. Introduction paragraph 5: Consider rephrasing as follows: “…providing empirical support for the claim that an MSM approach is appropriate for observational studies of antihypertensive medication use.”

10. Methods paragraph 2 (and Discussion paragraph 9): What proportion of visits used in the analysis had values for study variables imputed by last-value-carried-forward? Would there have been any advantage or disadvantage to using multiple imputation for the missing values?

11. Methods paragraph 6: Consider rephrasing as follows: “The effect of aggressive antihypertensive treatment on the risk of the primary outcome was assessed adjusted for time-dependent SBP using a Cox proportional hazards regression with combined stabilized weights (i.e., a marginal structural Cox model), as well as unadjusted for time-dependent SBP using a Cox proportional hazards regression without weights (i.e., a standard time-dependent Cox model).”

12. Methods paragraph 7: Could a figure be useful for illustrating the weighting and the pseudo-population?

13. Discussion paragraphs 11, 12, and 13: These paragraphs address methodological aspects of the MSMs, so it might be appropriate to briefly mention these issues in the Methods section.
14. Discussion paragraph 13: Does the minor violation of the assumption of equally spaced observations matter? What effect would this have had on the estimates?

Minor issues not for publication

15. Abstract: In the Methods section add the word ‘in’: “… prospectively enrolled in the …”

16. Introduction paragraph 5: Consider breaking the long sentence into 2-3 shorter sentences.

17. Introduction paragraph 6: Delete the first word ‘of’: “… be introduced by of the use of standard methods.”

18. Methods paragraph 1: Add the word ‘mean’ if correct: “… with no difference in mean BP between treatment strategies …”

19. Methods paragraph 8: Change ‘more narrow’ to ‘narrower’: “… to produce narrower confidence intervals …”

20. Discussion paragraph 10: Consider rephrasing “… an active area for future research in this area.” because using the word “area” twice seems redundant.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.