Author's response to reviews

Title: The time course of subsequent hospitalizations and associated costs in survivors of an ischemic stroke in Canada

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Author's response to reviews: see over
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Melissa Norton, MD
Editor-in-Chief
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Dear Dr. Norton,

Manuscript Title: The time course of subsequent hospitalizations and associated costs in survivors of an ischemic stroke in Canada.

Manuscript ID: 1722981184943716

We would like to thank the reviewers and the editors for the assessment of our manuscript referenced above. We have reviewed the comments and revised the manuscript per your request. These changes are highlighted for your reference. In this letter, we provide a response to each of the comments made by the reviewers.

Thank you for your reconsideration of this manuscript. We look forward to hearing from you soon.

Sincerely,

J. Jaime Caro, MDCM, FRCPC, FACP
Reviewer 1 (R1): Charles Wolfe

Major Compulsory Revisions

1. Clarification in abstract, methods and discussion about what the definitions are for stroke and cardiovascular disease. It is not clear whether the model looks at first or any strokes, and whether TIAs are included for those individuals who are then followed up. If they are the analyses should really be broken down into the 3 elements. If it is all strokes, be they first or subsequent a discussion of this weakness has to be introduced into the discussion as they have different natural histories and consequently resource use patterns. TIAS should be excluded or analysed separately.

Reply: The definitions for stroke and cardiovascular disease have been clarified on pages 5-6 of the Methods. TIAs are not included in selecting the population for analysis. The text in the Abstract and Methods sections has also been edited to clarify this point. On pages 11-12 of the Discussion, text has been added to address the issue of first versus subsequent strokes.

2. The abstract needs to be rewritten in light of the comments elsewhere in this review. for example in line 2 of the results they mention strokes and TIAs is this all strokes and if TIAS included these need to be analyzed separately if at all-the paper is about stroke. Line 4 what is the definition of cardiovascular? The final line of the conclusion is aspirational and not relevant to this analysis – i.e., to use the model to look at economic efficiencies.

Reply: Line 2 of the abstract has been revised and other revisions have been made in the abstract to address the reviewer’s comments as appropriate. The final line of the conclusion has been deleted. Regarding the definition of hospitalization due to cardiovascular disease, this has been added to the Methods section of the Abstract.
3. The methods section requires close attention to definitions as it is unclear to the reader what the actual variables mean.

Reply: The Methods section has been revised on page 6 to clarify the definitions of the variables that were considered.

4. p 6 para 2 last line - TIAs in hospital for 9 days are unlikely to be TIAs - especially in the mid 90s. Is this a coding error?

Reply: Yes, it is possible that this is a coding error; however, it is not possible to be certain of the extent of this. A study published in Stroke, 2005 estimated that 70% of TIAs reported in the Calgary region of Alberta province were coded correctly. This point has been added to the Discussion on page 12.

5. p 7. Predictors. Can the authors describe where the data are derived-past medical history? And what are definitions/validity? The authors refer in text to bleeding and haemorrhage-what is this? Is it related to warfarin treatment?

Reply: A paragraph has been added to the Methods section (page 6) to explain in more detail how these data were obtained and defined. The definition of bleeding events is also provided on page 6 of the Methods section. As clinical information such as cause of event is not available in the Saskatchewan data sets, it is not possible to confirm whether these events are due to warfarin therapy. The validity of these definitions highly depends on the accuracy of coding ICD-9 codes. The Discussion addresses this issue on page 12 and provides references to the documented validity of the Saskatchewan data.

6. Table 1 does not really provide much insight for the paper and could be removed

Reply: At the request of the reviewer, this table has been removed from the manuscript and the information incorporated into the text on page 6.
7. Table 2 the ICD codes need defining for the general reader. What is the relevance of describing risk factor %s for this paper. Can this be removed? Tables 8-10 are rather difficult to interpret-can labels at the top be clearer.

**Reply:** The ICD-9 codes have been defined in Table 2 at the request of the reviewer. The proportions of patients with each risk factor are provided as these are the predictors employed in the predictive modeling reported in the paper. It is not clear to us which tables the reviewer refers to as the submitted paper provided only Tables 1-5.

**Reviewer 2 (R2): Robert Kaplan**

**Major Compulsory Revisions**

**Abstract**

1. Specify that only hospitalized strokes were included

**Reply:** Strokes were identified both in the hospitalization and physician services files. The Abstract has been edited to clarify the selection of patients.

2. "Lengths of stay ranged..." It is unclear what is meant by "high" and "low" figures in this statement.

**Reply:** This phrase has been deleted from the Abstract as there is not sufficient space allowed to provide further explanation.

3. "Close-fitting Weibull functions..." This statement appears to describe Methods rather than Results

**Reply:** This statement describes the form of functions that were derived from our data analysis rather than the a priori methods used to define them. Thus we have left this statement in the Results section.
4. "Though these rates drop after one year..." The data supporting this conclusion should be described in Results section of Abstract.

**Reply:** These results have been added to the Results section of the Abstract.

**Methods**

5. Page 4: This study appears to have been limited to hospitalized strokes. This needs to be clarified in the description of subject identification and throughout the manuscript.

**Reply:** Please see previous response regarding this topic. The Methods (page 5) have been edited to clarify the selection of patients.

6. Page 4: ICD9 code 436 ("acute, ill-defined") was by far the most frequent code among stroke patients, which differs from prior studies cited on ICD9 codes for stroke. This should be noted, as code 436 is somewhat less accurate than other commonly-used ICD9 codes for stroke (eg, 434). Use of 362.3 (retinal vascular occlusion) to identify stroke is questionable, albeit this code was relatively uncommon

**Reply:** We reviewed the literature related to this issue and have found that ICD-9 is commonly coded for stroke admissions.

7. Page 5: In the description of the longitudinal models (Weibull and Cox PH), it should be stated whether and how death was used as a censoring variable.

**Reply:** Text explaining how these analyses were carried out has been added to the Methods section (page 6).

**Results**

8. Page 6: While the mean age was 71 years old, it is misleading to state that this patient population was “elderly” as the lower age limit was 21.

**Reply:** This statement has been edited to more accurately reflect the patient population.
9. Page 6-7: The description of the approach to estimating "Total Rate (TR)" parameter belongs in Methods, not Results.

Reply: The total rate is a result of the predictive modeling of these data, thus, we have left it in the Results section. As noted in response to a previous comment, the resulting equation was not defined a priori. The formula has been edited on page 8 to clarify this.

10. How did the hospitalization rates for subsequent non-cerebrovascular CVD, such as coronary disease/acute MI, compare with the rates in Table 5 for stroke and TIA?

Reply: These rates were considerably lower than those for TIA and stroke. A sentence reporting this finding has been added on page 9 of the Results section.

11. No information is presented on use of CV preventive medications (antihypertensives, coumadin, aspirin, lipid-lowering medications, etc). Except perhaps for aspirin, this information should be available from the prescription files which are described on page 4. In terms of generalizing these results to other populations, it would be critical to know how widely effective therapies were applied in this population.

Reply: These data have been added to the Results on pages 7-8.

Discussion

12. Page 8-9: The authors cite several prior studies describing the clinical course of stroke patients (refs 20-22), but they should also discuss the results of the present investigation in the context of these prior studies. Do the results presented here lead to substantially different conclusions, and if so why?

Reply: This comparison has been added to the Discussion on page 11.

13. Page 10: The observation that hospitalization rates after stroke were higher than those in a prior study of MI is interesting. What is the citation?

Reply: Thank you for noting this. It was a typo – MI events were higher – that has been corrected in the text. These are results are from unpublished analyses from the same data set.
Reviewer 3 (R3): Peter U Heuschmann

Major Compulsory Revisions

1. Why did the authors used 65y of age as cutoff-point for analysing the effect of age as predictor on hospitalizations in the COX model?

Reply: This age cut-off was used to correspond to point at which the health care and insurance coverage changes in the health care system in Canada.

2. A substantial proportion of patients (24%) already suffered from previous stroke prior to the index event for which they were included in the analyses. As the natural course of stroke (e.g. recurrence and survival rates) differs between first and recurrent strokes it might be worth to run analyses also separately for patients without prior history of stroke.

Reply: This is an interesting suggestion. We have included stroke as a covariate in the proportional hazards regression to take this into account. These results are reported in the Predictors section of the Results (page 8). This section has been revised to more clearly state the impact of a history of stroke on hospitalization. Comments have also been added to the Discussion to address these results (page 10).