Author's response to reviews

Title: Warfarin Use in Hemodialysis Patients with Atrial Fibrillation: Decisions based on Uncertainty

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Author's response to reviews: see over
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Dear Sir/Madam,

Thank you for the suggestions regarding “Canadian Society of Nephrology Survey confirms clinical equipoise for using warfarin in hemodialysis patients with atrial fibrillation” (MS ID: 1544678387775615) submitted for review to BMC Nephrology.

A number of revisions have been made:

1. **Authors’ Contributions** have been added, after **Competing Interests**.
2. **Acknowledgements** have been added, after **Authors’ Contributions**.
3. **Table 1** has been removed from the image uploads and now appears in the manuscript document after the **References**.
4. The titles and legends from **Figure 1** and **Figure 2** have been removed. **Figures 1 and 2** have been uploaded into the correct image slot.
5. Regarding reviewer 1 (Guido Finazzi) comments:
   - In **Discussion** lines 7-8, the statement that “previous gastrointestinal bleed was perceived as *higher* risk than a patient at risk for falls” has been corrected to “previous gastrointestinal bleed was perceived as *lower* risk than a patient at risk for falls.”
   - A statement regarding the novel oral anticoagulants has been added to the last paragraph, starting at line 6 of the **Discussion**.

   “Secondly, newer novel oral anticoagulants were not considered in our survey. However, while data on warfarin use in hemodialysis patients is limited, data on novel oral anticoagulant use is nonexistent; thus, warfarin is likely to remain the standard of care in this clinical setting for the foreseeable future.”

6. Regarding reviewer 2 (Patrick Saudan) comments:
   - “Most of the nephrologists come from Ontario and Quebec. Is this sample truly representative of the whole Canadian renal physician’s community?”
   - The authors feel that the survey respondents’ province of origin well represents the Canadian population base. A statement has been included in the discussion to reflect this, in light of the 2011 Canadian census data, now referenced.

   “The majority of respondents practiced in Ontario (54.4%) or Quebec (15.8%), in keeping with the large population bases of these two provinces, where 62.0% of Canada’s population resides [23].”
7. Regarding reviewer 3 (Simonetta Genovesi) comments:

MINOR revisions

The acronyms CHADS2 and CHA2DSVASC are now written correctly.

The background section has been updated. While Olesen’s paper has been included, the authors feel that it does not help to determine if and when the risk/reward balance is met in hemodialysis. A minority of patients in Olesen’s study (less than 1%) were on hemodialysis, and there is insufficient data to determine when a clinician chose to anticoagulate hemodialysis patients.

We have changed “The survey was sent three times within 6 weeks, at 2 week intervals” to “The identical survey was sent three separate times within 6 weeks, at 2 week intervals. Only one response per respondent was permitted.”

The duplicate reference for Wizemann V, Tong L et al has been deleted. This was previously references 5 and 22, and is now reference 6.

MAJOR revisions

1. Dr. Genovesi suggests that since warfarin is now available off patent, that pharmaceutical industries would not be interested in a randomized controlled trial, meaning funds would not be available to perform such a study. However, we feel a randomized trial is plausible since an area of such equipoise warrants publicly funded support for a randomized controlled trial (RCT). There are countless examples of such publicly funded trials; the Canadian Institute of Health Research funded 367 non-RCT and 33 RCT in 2011. The National Kidney Foundation provided $2,291,243 between July 1, 2011 and June 30, 2012 for various clinical research projects. It is thus plausible that pharmaceutical company money is not required to pursue an RCT in this clinical area.

2. Dr. Genovesi suggests that “it is obvious that when nephrologists, who have to deal every day with the difficult choice of whether or not prescribing warfarin without the help of any guidelines, are asked in a generic way if they are in favour of an RCT, they will answer that they would be happy with any RCT that might help them with their decision.”

We agree with the reviewers comment, and would like to reinforce that this “difficult choice” will continue to remain a “difficult choice” so long as there is no RCT on the topic. Identifying clinical equipoise is a crucial requirement before
designing and pursuing ethical RCTs, and it is thus reassuring that such equipoise exists.

3. Dr. Genovesi raises the concern that clinicians may be reluctant to enter their patients into a RCT, in light of the possibility that patients at high risk for bleed may be given warfarin, or that patients at high risk for stroke may be withheld warfarin.

These are important concerns. Dr. Genovesi has formulated several questions which will need to be addressed in future surveys, especially in the buildup to writing a grant application to fund an RCT on this topic. We thank Dr. Genovesi for her raising these questions, which will be addressed in upcoming surveys.

Yours sincerely,

Dr. Benjamin Thomson
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