Author's response to reviews

Title: Use of Warfarin in Long-Term Care: A Systematic Review

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Author's response to reviews: see over
Feb. 26, 2012 revision: In response to the BMC editor request of Feb. 8, 2012, we made the specific responses noted below for “Editorial Requests” and highlighted in the manuscript in red. No further revisions were made to the draft of the revised manuscript that we had sent to BioMed Central Editorial on January 26, 2012.

Editorial Requests:

1) Please ensure that your abstract contains context information about your study in the background section (http://www.biomedcentral.com/bmcgeriatr/authors/instructions/researcharticle#formatting-abstract).

We added this additional content to the background section of the abstract:

“The use of warfarin in older patients requires special consideration because of concerns with comorbidities, interacting medications, and the risk of bleeding. Several studies have suggested that warfarin may be underused or inconsistently prescribed in long-term care (LTC);”

To maintain the 350 word-count limit, we made some minor revisions to the abstract and removed this sentence from the results section of the abstract:

“Therapies and resident characteristics positively associated with stroke prevention were warfarin in residents with AF and history of stroke (vs no stroke), warfarin or antiplatelets in stroke survivors with AF (vs no AF), and warfarin or antiplatelets in stroke survivors with hypertension or depression.”

2) Please ensure that your Competing interests section contains all the potential relevant financial, funding, and commercial interests. This includes all private companies which you have a stake in and all sponsorship of the study.

The questions that are asked of authors are:

Financial competing interests
- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests
- Are there any non-financial competing interests (political, personal, religious, academic, ideological, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

We revised the Competing Interests section to more fully comply with each item listed above.

Referee 1 Comments
1. The study is a comprehensive and thorough review concerning the use of warfarin in LTC. I have no major comments or concerns.

Referee 2 Comments

1. This is a detailed and well written review on the use of anticoagulant therapy in LTC. The work is well organized and the literature updated. The authors addressed a very important, although difficult, issue in geriatric medicine. I have only one major concern that relates with conclusion reported both in the abstract and in the text.

The authors concluded that the suboptimal prescription of warfarin in LTC is likely to be associated with substantial adverse consequences for patients, families, hospitals, and payers. I believe that a careful estimate of the benefit/risk ratio of this therapy among the oldest old is very difficult. Furthermore, this aspect was not specifically addressed over the literature review process, and therefore this conclusion is not supported by the results presented and looks a little out of the contest. The authors should consider to revise the paragraph and at least attenuate a bit their conclusions.

We agree with the reviewer. We made the following changes:

Page 3, Abstract, final sentence

Replaced

"Conclusions: Among residents with AF, use of warfarin and maintenance of international normalized ratio levels to prevent stroke are suboptimal. Among prescribers, perceived challenges associated with warfarin therapy often outweigh its benefits. Nevertheless, in LTC residents, consequences of no or suboptimal therapy are likely to be substantial."

with

"Conclusions: Among residents with AF, use of warfarin and maintenance of international normalized ratio levels to prevent stroke appear to be suboptimal. Among prescribers, perceived challenges associated with warfarin therapy often outweigh its benefits. Further research is needed to explicitly consider the appropriate balancing of risks and benefits in this frail patient population."

Page 24, Conclusions, final sentence

Replaced

“The harm of anticoagulant underuse has not been estimated in LTC. However, evidence from this review suggests that the adverse consequences of suboptimal therapy to residents, their families, hospitals and payers, are likely to be substantial.”

with

“Further research is needed to evaluate appropriate use of anticoagulants in this setting, including a more explicated consideration of the appropriate balancing of risks and benefits in an important but problematic issue for the geriatric clinician.”

2. Page 10, line 9: ?Lapane et al?. did not increased significantly following the introduction of clopidogrel?..is not clear to me. Why should warfarin use increase after the introduction of a new antiplatelet agents? Please, clarify or delete this sentence.

We agree that this needs further explanation. We made this change:
“Comparing data from 1997 and 2000, Lapane et al. [19] found that the use of warfarin for the secondary prevention of ischemic stroke did not change significantly following the introduction of clopidogrel, from 22% in 1997 to 23% in 2000, while antiplatelet use did increase from 41% in 1997 to 48% in 2000.”

with

“Lapane et al. [19] evaluated, among stroke survivors, whether introduction of a prospective payment system (PPS) that required nursing homes to bear the cost for warfarin monitoring had shifted utilization from warfarin to antiplatelet agents. Comparing data from 1997 and 2000, Lapane et al. [19] found that the use of warfarin for the secondary prevention of ischemic stroke did not change significantly following the introduction of the PPS, from 22% in 1997 to 23% in 2000, while antiplatelet use did increase from 41% to 48% over the same period (likely due to the introduction of clopidogrel).”

3. Page 11, the ORs of 50.95 (line 5) and 1.06 (line 16) are non consistent with the reported 95% CI.

Regarding the latter OR (line 16), we corrected “(OR=1.06, 95% CI=1.02–11.1)” to “(OR=1.06, 95% CI=1.02–1.11)” per the Quilliam et al. article.

Regarding the former (line 5) error from the Abdel-Latif et al. study, we have just received a correction from the author that the odds of NOT prescribing warfarin in residents with prior stroke was “OR=CVA 0.203 (95% CI 0.087 to 0.474).” To make the direction of this relationship (toward prescribing of warfarin) consistent with the other reviewed studies, we apply the inverse of this value. Thus, for Abdel-Latif et al., we have OR=4.93, (95% CI 2.11 to 11.49) for odds of prescribing warfarin.

At this location, we have also corrected the rounding of the Gurwitz et al. OR, and have replaced

“Among residents with AF in LTC facilities, Abdel-Latif et al. [7] (OR=50, 95% confidence interval [CI]=2.1–11.1) and Gurwitz et al. [8] (OR=1.87, 95% CI=1.2–2.91), found a positive association between having a history of stroke and receiving warfarin;”

with

Among residents with AF in LTC facilities, both Abdel-Latif et al. [7] (OR=4.93, 95% confidence interval [CI]=2.11–11.49 [correction provided by these authors]) and Gurwitz et al. [8] (OR=1.87, 95% CI=1.20–2.91), found a positive association between having a history of stroke and receiving warfarin.

A corresponding change for Abdel-Latif et al. was made in page 2 (Table 2) of the tables document, “OR=50 (2.1-11.1)” has been changed to “(OR, 4.93; 95% CI, 2.11-11.49)”

4. Page 15, line 6: ??low sample size? should read small sample size?.

Changed “Four studies [7, 9, 17, 21] had low sample sizes” to “Four studies [7, 9, 17, 21] had small sample sizes.”

5. Page 15, line 22: ??chronic AF should read permanent FA?.

This sentence currently reads: “In a similar study, Monette et al. [29] used two case studies – a 94-year old male with chronic AF and co-morbid CHF but having independent physical function and no fall history…”

We’ve referred back to the ACC/AHA/ESC 2006 guidelines* to help clarify the issue of AF nomenclature. These guidelines suggest classification of AF based on pattern of presentation including “recurrent paroxysmal AF,” “recurrent persistent AF,” and “permanent AF.” [p. e327-e328]. The guidelines also state
that “[A]ssorted labels have been used to describe the pattern of AF, including acute, chronic, paroxysmal, intermittent, constant, persistent, and permanent, but the vagaries of definitions make it difficult to compare studies of AF or the effectiveness of therapeutic strategies based on these designations.” [p. e265] Since, in their 1997 article, Monette et al. used the term “chronic” without further elaboration, for instance whether this would include permanent AF alone, or either recurrent persistent or permanent AF, we are inclined to maintain Monette et al.’s original usage of “chronic.”