Author's response to reviews

Title: Prostate cancer-specific survival among warfarin users in the Finnish Randomized Study of Screening for Prostate Cancer

Authors:

Pete Kinnunen (Kinnunen.Pete.T@student.uta.fi)
Teemu Murtola (Teemu.Murtola@uta.fi)
Kirsi Talala (Kirsi.Talala@cancer.fi)
Kimmo Taari (kimmo.taari@helsinki.fi)
Teuvo Tammela (Teuvo.Tammela@uta.fi)
Anssi Auvinen (Anssi.Auvinen@staff.uta.fi)

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Author’s response to reviews:

We are thankful for your interest in our manuscript. We have carefully revised it according to the reviewers’ comments. Please find our detailed responses to each comment below. We hope you find the revised manuscript suitable for publication.

Sincerely,

Pete Kinnunen
Teemu J Murtola
Kirsi Talala
Kimmo Taari
Teuvo LJ Tammela
Anssi Auvinen

Response list
Reviewer 1:

1. pg. 5, line 75 Authors should describe how the baseline for this study was defined (i.e. date of diagnosis? date or treatment?)

RESPONSE

- Baseline is defined as time of the FinRSPC randomization which is further explained in the next sentence. To clarify this we have added to the following clarification to Methods, Study cohorts, 1st sentence:

“FinRSPC includes 80,458 men aged 55-67 years at baseline (i.e. at FinRSPC randomization)”

2. How was active surveillance in men with prostate cancer defined? Did it also include men managed with watchful waiting?

RESPONSE

- Yes, it includes all men whose primary treatment was expectant management, be it active surveillance or watchful waiting. We now clarify this in the manuscript:

“We also collected information on primary therapy of PCa (radical prostatectomy, external beam radiation therapy (EBRT), hormonal therapy or active surveillance/watchful waiting”

3. The authors need to be consistent with the use of abbreviations in this paper (e.g. prostate cancer abbreviation has not been used consistently).

RESPONSE

- Excellent notion. We have revised the manuscript and altered ‘prostate cancer’ to ‘PCa’ to be consistent with abbreviations.

4. pg. 8, line 155. p-levels should be stated

RESPONSE

Thank you for this comment. However, we prefer to report 95% confidence intervals instead of p-values as they are more informative, giving an idea of statistical precision in addition to statistical significance. To keep the style of manuscript uniform we have not added p-value to this one point. In the competing risks analysis (Fine and Gray regression analysis) the P value was 0.724 which we did not include in the manuscript as explained above.

5. Results. pg. 9 line 172. Authors state that a pre-diagnostic use of warfarin for 5 years or more was associated with a significant risk increase. Although the HR indicates the increase, statistically this is not significant (but it may be clinically, which needs to be discussed). The
remaining HR values and their CIs in the manuscript need to be revised and their significance appropriately addressed as well.

RESPONSE

-It is true that the risk increase by pre-diagnostic warfarin use is strictly speaking not statistically significant, but very close. Therefore we have used term “borderline significant”:

“However, pre-diagnostic use of warfarin for 5 years or more was associated with a borderline significant risk increase in the multivariable-adjusted model (HR 1.49, 95% CI 0.97-2.28)” Borderline significant does not mean statistically significant.

We have reviewed the use of expression ”significant” in our manuscript.

6. It would be good to know what proportion of men actually had VTEs. This hasn't be listed anywhere in the manuscript.

RESPONSE:

-This information is covered in Table 1 under heading “Thrombotic factors”. Our data on diagnoses of thrombotic events came from national hospital discharge registry. Therefore these were mainly pulmonary embolisms. VTEs are usually managed in the primary care, and their number was low in our data, only 48 cases. Therefore VTEs were categorized together with other thrombotic events.

7. Authors should include more information about the registry and to discuss it again other similar setting in the world. Ability to link registry data with the other large datasets is a strength of this study which also needs to be discussed accordingly.

RESPONSE

Thank you for this comment. We fully agree. We have extended description of the registries in the Methods-section, with appropriate references for those who wish to get further knowledge.

We now also mention our ability to use comprehensive national registry information as strength of our study.

8. Table 1 - appropriate significance tests between the groups would be beneficial.

RESPONSE:

We have added footnotes denoting statistically significant P-values for differences between anticoagulant users and non-users in Table 1.
Introduction: The investigation is justified by a few prior investigations showing that Warfarin intake might modify mortality among prostate cancer (PCa) patients.

RESPONSE

- Thank you for this comment. We fully agree.

Methods: The study examines effects of Warfarin and other anticoagulants on mortality in men diagnosed with incident prostate cancer in a large cohort of Finnish men. Statistical methodology (Cox regression, sensitivity analysis and lagged analysis) appears to be appropriate.

RESPONSE

- Thank you for this comment. We fully agree.

Results: The study investigated the effect of warfarin and other anticoagulants on mortality in 6,537 men diagnosed with prostate cancer (PCa) during 1995-2009 within a cohort of 80,458 Finnish men. Post-diagnostic use of low dose low intensity warfarin was associated with an increased risk of PCa death (overall HR 1.47, 95% CI 1.13-1.93). However, no risk increase or decrease was observed among short term users or among high-intensity users in a lagged analysis of the data. The tables of results are complete and provide adequate information for checking the rigor of statistical methods used.

RESPONSE

- Thank you for this comment. We fully agree.

Discussion: The study observed elevated risk of PCa death with short term use of Warfarin "which is probably explained by a higher risk of thrombotic events prompting warfarin use in patients with terminal PCa."

This in fact is a form of "protopathic bias" as described by Horwitz and Feinstein in their classic paper. The authors should acknowledge this important paper and source of bias in the epidemiologic literature.

RESPONSE

- Excellent addition to the article. We have added the following sentence and reference to the end of 1st paragraph in discussion where the aforementioned phenomenon is discussed:

- “In epidemiological literature this phenomenon where pharmaceutical drug is prescribed for early manifestation of yet un-diagnosed disease is referred to as ‘protopathic bias’ [25].”

- Additionally, numbering of references has been revised after addition of this new reference.

**Conclusion:** The conclusion of the report appears to be justified by the results. In a population-based setting, warfarin or other types of anticoagulants are not associated with improved prostate cancer prognosis. Conversely, in short-term use risk of PCa death was increased, which is most likely due to thrombosis caused by an advanced cancer, as the risk increase was not observed in long term.

**RESPONSE**

- Thank you for this comment. We fully agree.