PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Discontinuation of statin therapy in the elderly – does a cancer diagnosis make a difference? An observational cohort study using data linkage
AUTHORS	Efty Stavrou, Nicholas Buckley, Jake Olivier and Sallie-Anne Pearson

VERSION 1 - REVIEW

REVIEWER	Peter Hall Clinical Research Fellow in Medical Oncology University of Leeds UK
REVIEW RETURNED	02/02/2012

THE STUDY	I found the statistical analysis section slightly confusing. "Censor dates were the date of last statin dispensing before discontinuation." Does this mean that all discontinuations were censored? I can't believe this was the case because then you would have no discontinuation events. Perhaps this could be re-worded? Could more information be provided on the relationship between prescribing and dispensing in the Australian system? e.g. Is there a maximum time that dispensing can continue without renewal of a prescription by the prescribing clinician?
RESULTS & CONCLUSIONS	The discontinuation 'rate' implies to me the rate of discontinuation over a discrete time interval. It could be made clearer in a number of places when the athours mean rate, over what time interval they refer to. In a number of places referring to the 'proportion discontinued' at a given follow-up time might be clearer. It would also make more sense to me if Figure 2 showed the actual Kaplan-Meier plot rather than just joining dots. Numbers at risk would also be interesting. Should the two curves be compared with a log-rank test? Table two is great but I would find it easier to interpret if presented as a forest plot.
GENERAL COMMENTS	This is a great paper which informs an important and neglected question. I think it would be appropriate to make your conclusions stronger - I think your results make a good case that statins are inappropriately continued in cancer, at least in some patients. Your Cox regression suggests prognosis does influence discontinuation decisions, but would it be possible to emphasise this point by plotting survival in patients who do and do not discontinue statins in the first 6 months after diagnosis in the cancer cohort? If the curves are similar then this would suggest that clinicians are ignoring the decision on whether or not to continue statins on the

	basis of expected prognosis.

REVIEWER	Tawee Tanvetyanon MD Associate Member H. Lee Moffitt Cancer Center and Research Institute Tampa, FL USA No competing interests
REVIEW RETURNED	10/02/2012

THE STUDY	There is a major problem with statistical method.
RESULTS & CONCLUSIONS	Conclusion in the abstract is not based on the results
GENERAL COMMENTS	This is an interesting analysis using a very large database from Australia. The study provides insight into the practice of statin discontinuation. However, the paper is weak for a number of reasons. 1) Conclusion in the abstract is not necessarily based on the study results. 2) Statistical method is a major concern. -In order to account for clustering of subjects, the analysis will need to use Cox model stratified by matched pair. This will result in less efficiency and it is possible that many findings in the study will become statistically insignificant. -The evidence of well matched was not presented. In fact, after the match, it appears that the authors need to use regression to adjust for some covariate imbalances between the study group and the control group. -No justification provided for matching by age and gender. 3) Patients in the cancer group were not necessarily those with advanced disease. Many patients evidently survive many years, greatly detracting from the initial justification the authors were trying to make regarding statin discontinuation.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. I found the statistical analysis section slightly confusing. "Censor dates were the date of last statin dispensing before discontinuation." Does this mean that all discontinuations were censored? I can't believe this was the case because then you would have no discontinuation events. Perhaps this could be re-worded?

We have reworded the sentence to ‘Follow-up continued until last statin dispensing date before discontinuation, December 31, 2009 or date of death’. (pg 6, para 2)

2. Could more information be provided on the relationship between prescribing and dispensing in the Australian system? e.g. Is there a maximum time that dispensing can continue without renewal of a prescription by the prescribing clinician?

We have added the following detail to the ‘setting’ section of the methods. (pg 5, para 1):
‘In the Australian setting chronic medicines including statins are generally prescribed as a month supply with five repeats’.

3. The discontinuation 'rate' implies to me the rate of discontinuation over a discrete time interval. It could be made clearer in a number of places when the authors mean rate, over what time interval they refer to. In a number of places referring to the 'proportion discontinued' at a given follow-up time might be clearer.

We have changed the wording according to the reviewer's suggestion in the following sections:
• pg 2, abstract
• pg 7, para 4
• pg 8, para 2

4. It would also make more sense to me if Figure 2 (1?) showed the actual Kaplan-Meier plot rather than just joining dots. Numbers at risk would also be interesting. Should the two curves be compared with a log-rank test?

Our aim with the figure is to highlight differences in proportion of patients discontinuing statin therapy at specific time points. Therefore, we believe that the figure which was part of the original submission better reflects our aim than a Kaplan-Meier plot. However, we have included the graph suggested by the reviewer at the end of this document (Alternative to Figure 1) should the editorial team prefer to use it. The log-rank p-value has been included (page 7, para 3), as have numbers at risk at each time-point (Figure 1 and Alternative Figure 1).

5. Table two is great but I would find it easier to interpret if presented as a forest plot.

The data is now presented in Figure 3.

6. This is a great paper which informs an important and neglected question. I think it would be appropriate to make your conclusions stronger - I think your results make a good case that statins are inappropriately continued in cancer, at least in some patients.

We have added this point to the abstract (pg 2) and discussion of the manuscript (pg 8, para 3).

7. Your Cox regression suggests prognosis does influence discontinuation decisions, but would it be possible to emphasise this point by plotting survival in patients who do and do not discontinue statins in the first 6 months after diagnosis in the cancer cohort? If the curves are similar then this would suggest that clinicians are ignoring the decision on whether or not to continue statins on the basis of expected prognosis.

We have now included the (overall) survival curves for cancer patients surviving 6 months from diagnosis according to those who did and did not discontinue statin therapy at the time (Figure 4). We have also described the figure in the methods (pg 6, para 2) and results sections (pg 8, para 1) and redrafted the discussion to reflect this finding (pg 9, para 1).
Reviewer 2:
This is an interesting analysis using a very large database from Australia. The study provides insight into the practice of statin discontinuation. However, the paper is weak for a number of reasons.

1. Conclusion in the abstract is not necessarily based on the study results.

We have revised the conclusions in the abstract to incorporate the suggestions of both reviewers (pg 2).
'Medications should be rationalised at the time of a cancer diagnosis, especially in the setting of a poor prognosis. At least for some patients in our cohort, statin therapy may be inappropriately continued which adds unnecessarily to therapeutic burden'.

2. Statistical method is a major concern.
-In order to account for clustering of subjects, the analysis will need to use Cox model stratified by matched pair. This will result in less efficiency and it is possible that many findings in the study will become statistically insignificant.

The statistical analysis comparing the cancer cohort with their matched comparisons was conducted using a stratified Cox Proportional model, but due to brevity in the previous version of the manuscript, this was not made clear. The description of the analysis has been amended (page 6, last para):
'We used Cox regression to compare discontinuation between cohorts, stratifying by cancer patients matched to their controls (prior hospitalisation was included as a covariate due to difference between the cohorts after matching).'

-The evidence of well matched was not presented.

- In fact, after the match, it appears that the authors need to use regression to adjust for some covariate imbalances between the study group and the control group.

The cancer and comparison cohorts were matched on age, gender and previous statin use. The only characteristic which differed after matching was that the cancer cohort had fewer hospital admissions than their matched counterparts. The methods section has been amended to more accurately reflect our statistical approach (page 6, last para). The cohort characteristics were described in the opening paragraph of the results in the original submission (pg 7).

The cancer cohort was modelled separately to ascertain the effect of cancer-specific factors on statin discontinuation using multivariate Cox Proportional hazard regression. We have added clarification into the methods (page 6, last para):

For the cancer cohort, we used Cox Proportional hazard regression to determine the factors associated with discontinuation following a cancer diagnosis.....

-No justification provided for matching by age and gender.

We have added the justification of the age and gender matching (page 6, para 1)

'Certain cancers are gender-specific and age-related. Further, statin discontinuation is age and gender-related by virtue of their relationship to cardiovascular risk factors.21 As such, we matched (using random selection without replacement) two clients with no evidence of a cancer notification to every cancer cohort member on year of birth (within five years), gender, a statin dispensing record within 15 days of the index date and first statin dispensing date (within 15 days) to match patients with comparable duration of statin treatment. Cohort members also were alive for at least six months after the index date.'

3) Patients in the cancer group were not necessarily those with advanced disease. Many patients evidently survive many years, greatly detracting from the initial justification the authors were trying to make regarding statin discontinuation.

Our overall objective was to use a cohort of cancer patients diagnosed at all stages of the disease to investigate whether or not cancer spread-of-disease was a factor considered for discontinuing statin therapy. We feel this enhances our research study, as to-date, previous research has focussed exclusively on patients with a poor prognosis. We have expanded on this issue in the discussion (pg 8, last para)

‘Research in this area to date has focused exclusively on cancer patients with end-stage diseases.1 5 6 However our methodological approach using a cohort of patients diagnosed at all stages of disease demonstrates clearly that there may be some recognition on the part of doctors and or patients that medications need to be rationalized in light of a poorer prognosis. In our cohort statin discontinuation was associated with a diagnosis of metastatic disease and poorer overall survival. Nevertheless, a large proportion of cancer patients were prescribed statins in the 30 days before death.’