PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Patients who discontinued statin treatment: a protocol for cohort study using primary care data
AUTHORS	Vinogradova, Yana; Coupland, Carol; Brindle, Peter; Hippisley-Cox, Julia

VERSION 1 - REVIEW

REVIEWER	Simon Thornley Counties Manukau District Health Board, New Zealand
REVIEW RETURNED	22-Jun-2015

GENERAL COMMENTS	This paper describes the methods of a cohort study which considers the 'survival' of people taking statins. I think the paper is generally well presented and described. I have two major concerns. The paper's introduction does not address the controversy about statin use, highlighted recently in the British Medical Journal by John Abramson and others. It also does not point to the literature which shows little evidence of benefit from the drugs, particularly in the area of primary prevention, such as the meta-analysis from Ray (Arch Intern Med. 2010 Jun 28;170(12):1024-31). The authors' introduction mainly references studies that support statin use, such as the CTT meta-analysis, and glosses over the controversy. In addition, the observational studies they point to generally support the assertion that statins are beneficial and stopping the drugs is associated with an increase in risk of event. Other studies, such as one by Darmuth show that statin users, or those that adhere, in the U. S., are generally at lower risk of events that are implausibly related to drug use, such as trauma related injury (Circulation. 2009 Apr 21;119(15):2051-7). The other concern I have relates to the methods. I note that death is, here, considered as an event that censors the individual during follow-up. I would have thought, that it would be important to consider, at least, in a sensitivity analysis, death as a competing risk, due to its clinical importance. Otherwise, I think the methods are sound and likely to yield an informative and interesting answer to the research question.

REVIEWER	Richard Lowrie NHS Greater Glasgow and Clyde Scotland
REVIEW RETURNED	21-Jul-2015

GENERAL COMMENTS	This is an important area and the authors are to be commended for this protocol and the way it is written. Many eventualities have been described and adequately accounted for. This reviewer would prefer to see the following (minor) changes, to improve reproducibility of the methods, and provide the context for interpretation of results: Abstract Limitation is the uncertainty of adherence to statin treatment rather than the possible uncertainty. Suggest use “adherence” or “compliance” rather than both at different points in manuscript. - Introduction. Does stopping a statin as described in the paper, mean the patient has stopped ordering the prescription from their practice / stopped picking up the prescription from their practice or stopped collecting the dispensed prescription from the pharmacy? I feel the authors should be clear on there being an unproven although intuitive link between stopping statins and non adherence on the one hand, and prescribing of statins and possible adherence on the other. This may not be clear to a wider audience and i feel it should be made clearer from the outset. If available, is there any reference to work that describes the link between P4. Line 10 “significant risk factors” typo in “factors”. Culminating in Line 42, may be worthwhile pointing out that the effect of statins may be mediated independently of changes to cholesterol levels. P5. Line 15 may be interpreted in a way that means the complexity of treatment unlikely to be a factor…suggest re-wording to convey the message that treatment complexity e.g. polypharmacy may contribute to non adherence and therefore discontinuation. - Methods Please provide full description of patient inclusion criteria. It reads as though CVD diagnosis during the study period will be reason for censoring. In the interests of clinical practice, those who

	develop CVD represent an interesting group. Would it not add to the usefulness of the study to follow those who develop CVD separately and report outcomes, rather than censor at that point? P9. May be worthwhile including QOF changes - Setting. Please elaborate on which practices, how, when, and what data appears in CPRD. While the website for CPRD is given, is there anything, for example that can be said about the representativeness of participating practices? May QOF participation/change in relevant indicators be a confounder? Is there any possibility that the number of different medicines prescribed for each patient, could be included in the analysis? Or the number of co-morbid conditions? Discussion Line 28 would benefit from a supporting reference. Line 36 – does this describe patients with CVD or not?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Simon Thornley
Institution and Country Counties Manukau District Health Board, New Zealand.

This paper describes the methods of a cohort study which considers the 'survival' of people taking statins.

I think the paper is generally well presented and described. I have two major concerns. The paper's introduction does not address the controversy about statin use, highlighted recently in the British Medical Journal by John Abramson and others. It also does not point to the literature which shows little evidence of benefit from the drugs, particularly in the area of primary prevention, such as the meta-analysis from Ray (Arch Intern Med. 2010 Jun 28;170(12):1024-31). The authors' introduction mainly references studies that support statin use, such as the CTT meta-analysis, and glosses over the controversy. In addition, the observational studies they point to generally support the assertion that statins are beneficial and stopping the drugs is associated with an increase in risk of event. Other studies, such as one by Darmuth show that statin users, or those that adhere, in the U. S., are generally at lower risk of events that are implausibly related to drug use, such as trauma related injury (Circulation. 2009 Apr 21;119(15):2051-7).

This is fair comment. We have added the paragraph below and slightly reordered the Introduction to make these fit.

“However, while statin therapy is associated with decreased mortality and fewer complications related to atherosclerosis for patients already diagnosed with CVD, this has not been established for patients without CVD. Statins also have side effects and a number of studies have demonstrated these[14], which include increased risks for diabetes[15 16] and myopathy[17 18]. With respect to their effectiveness in patients without CVD, a meta-analysis of eleven randomised controlled trials reported no significant associations between statin use and mortality risk for such patients (risk ratio 0.91, 95%CI 0.83 to 1.01).[19] A later meta-analysis, investigating the effect of cholesterol-lowering therapy on all-cause mortality, did show a significantly reduced risk for non-CVD patients (risk ratio 0.91, 95%CI 0.88 to 0.93).[4] However, as highlighted in a subsequent secondary analysis, this reduced mortality was not demonstrated for the subgroup with low cardiovascular risk (0.95, 0.86 to 1.04 for CVD risk <10%).[20] Moreover, the original finding might simply have reflected a healthy-user bias because a study investigating the risk of accidents associated with adherence to statins[21] has shown adherent patients to be less likely to be involved in accidents (hazard ratio 0.85, 95%CI 0.83 to 0.87) and more likely to use screening services (1.17, 1.15 to 1.20).”

The other concern I have relates to the methods. I note that death is, here, considered as an event that censors the individual during follow-up. I would have thought that it would be important to consider, at least, in a sensitivity analysis, death as a competing risk, due to its clinical importance.

This is an interesting point, but we have now considered it and decided for the following reasons not to include death as a competing risk. The aim of our study is not to compare risks of discontinuation between different groups of patients but to identify specific factors associated with the risk. So using competitive risks here would be inappropriate, because such an analysis would involve trying to estimate the effects of covariates on cumulative incidence of the outcomes, which might be very different for discontinuation and death. The other reason is that the results of such an analysis would not be generalisable, but limited to populations with similar characteristics and death rates. For our aim it is acceptable to ignore competitive risks and to use the Cox model for assessing which factors have a prognostic value for discontinuation. Such an approach will produce results valid for any population regardless of the death rate. [Pintilie M. Analysing and interpreting competing risk data. Statistics in Medicine 2007;26(6):1360-67]

Otherwise, I think the methods are sound and likely to yield an informative and interesting answer to the research question.

Reviewer: 2
Reviewer Name Richard Lowrie
Institution and Country NHS Greater Glasgow and Clyde

This is an important area and the authors are to be commended for this protocol and the way it is written. Many eventualities have been described and adequately accounted for.

Abstract
Limitation is the uncertainty of adherence to statin treatment rather than the possible uncertainty. Suggest use “adherence” or “compliance” rather than both at different points in manuscript.

We have made both corrections, removing the word “possible” and replacing “compliance” with “adherence”.

- Introduction.
Does stopping a statin as described in the paper, mean the patient has stopped ordering the prescription from their practice / stopped picking up the prescription from their practice or stopped collecting the dispensed prescription from the pharmacy?

We have clarified this, with the following changes to the text (Abstract and end of Introduction respectively):

"If there are no prescriptions within 90 days after the expected last date of a prescription, a patient will be defined as a stopper with the discontinuation outcome date as the expected finishing date."

"… report the rates of stopping for statins with the discontinuation outcome based on prescription data."

I feel the authors should be clear on there being an unproven although intuitive link between stopping statins and non adherence on the one hand, and prescribing of statins and possible adherence on the other. This may not be clear to a wider audience and i feel it should be made clearer from the outset. If available, is there any reference to work that describes the link between

We have added the following text and reference to clarify our thinking with respect to the first aspect of this intuitive link, but we do not see that the second aspect is an issue for us because we are not studying adherence (for which we have no data) but only possible reasons for discontinuation. We are not sure, however, if we have missed something because of the incomplete last sentence.

"The benefits of such preventive therapy are, however, dependent on the level of adherence of patients with their prescribed regime and discontinuation is an extreme form (zero adherence) of non-adherence[7]."

P4.
Line 10 "significant risk factors" typo in "factors".

We have corrected this.

Culminating in Line 42, may be worthwhile pointing out that the effect of statins may be mediated independently of changes to cholesterol levels.

We have amended the sentence as follows.

"Discontinuation of statins can cause changes in platelet activity or inflammation, impair vascular homeostasis or lead to endothelial dysfunction and may, therefore, independent of changes of cholesterol levels, increase risk of cardiovascular events."

P5. Line 15 may be interpreted in a way that means the complexity of treatment unlikely to be a factor…suggest re-wording to convey the message that treatment complexity e.g. polypharmacy may

contribute to non adherence and therefore discontinuation.

We have added the sentence:

“Statin therapy is also not in itself complex, although issues arising from polypharmacy or other patient needs might well cause discontinuation.”

- Methods
Please provide full description of patient inclusion criteria.

We have added that patients should be aged 25 to 84 “at the study entry”.

It reads as though CVD diagnosis during the study period will be reason for censoring. In the interests of clinical practice, those who develop CVD represent an interesting group. Would it not add to the usefulness of the study to follow those who develop CVD separately and report outcomes, rather than censor at that point?

We have changed the word “censoring” to “follow-up”. We have also added the sentence below to Statistical analysis:

“For patients in the primary prevention group who were diagnosed with CVD after entering the study, we shall report the percentages of patients who continued using statins after the diagnosis.“

P9. May be worthwhile including QOF changes

Thank you for this suggestion. The practices are not identifiable and QOF data are not linked. We have, therefore, included the practice id number as a clustering variable to account for any possible differences between the practices as noted below:

“Practices might differ in their prescription patterns, so we will account for clustering by practice.”

Setting. Please elaborate on which practices, how, when, and what data appears in CPRD. While the website for CPRD is given, is there anything, for example that can be said about the representativeness of participating practices?

We have added the following text and reference to a recent publication describing CPRD in detail, which included geographical distribution of the practices and age-sex representativeness of the registered patients.

“The practices are spread across the UK and their registered patients have been shown to be representative of the general population.[38]”

May QOF participation/change in relevant indicators be a confounder?

See response above.

Is there any possibility that the number of different medicines prescribed for each patient, could be included in the analysis? Or the number of co-morbid conditions?

We are already accounting for a number of comorbidities and we have also considered this point and added the number of different types of drugs as a proxy for co-morbid conditions to the analysis. In this context they also indicate whether if patients are already taking tablets they are more or less likely to be willing to take other tablets:

"…and – as a proxy for co-morbid conditions – the number of different types of medicines having systemic effect and associated with British National Formulary[39] categories (in each case, at least one prescription in the last year before the entry date)"

Discussion
Line 28 would benefit from a supporting reference.

We have added the reference:

Lemstra M, Blackburn D. Nonadherence to Statin Therapy: Discontinuation After a Single Fill. Can J Cardiol 2012;28(5):567-73

Line 36 – does this describe patients with CVD or not?

We have amended the text to clarify this as follows:

"These would appear as false stoppers, but a Health Survey for England has shown the proportion of patients using over-the-counter sources (restricted by licence to individuals with a 10–15% ten-year CVD risk) to be very low at 0.2%.[42]"