Reviewer #2: I thank the authors for their reply. However, their answer does not address my comment sufficiently. The newly provided reference from Weberpals et al. does not apply to your methods. This reference is addressing immortal time bias, which is not the focus of your study. Immortal time bias occurs when the timing of a specific treatment occurs at different times in the follow up and the impact of these differences are analzyed. But if I understand your analysis correct you wanted to test if the duration of statin intake or no intake of statin at all impacts your outcome. In your model statin use is modelled as a categorical variable in various ways, which is fine. In your comment you state:"Our main interest in this study was assessing the associations measured through cause specific hazards, which is valid in the presence of competing risks" But in your models I cannot see cause-specific hazard modelling. To me it looks like regular Cox models, where duration of statin use is modelled in a different way. But the reference from Austin that you provide explains why it is so important to adjust for the competing risk. If patients take statin someone may conclude that the risk for dying of e.g. cardiac disease is more likely because these patients will take statin because of high blood cholesterol, thus these patients have a higher risk for dying form heart attack, which results in a lower risk dying from prostate cancer. This said, the model predicting prostate cancer specific mortality, needs to be adjusted for the competing risk (other-cause of death), using the Fine-Gray hazard or the cause-specific hazard model. Also, please report the time-point of the HR in your results.

Firstly, it is important to clarify that there are two important time components in our study: the time to the outcome of prostate cancer or biopsy and the time a patient remains unexposed to statins and then becomes exposed to statins. The first is a time-to-event outcome and the second is time-dependant covariate. These are two different time components and it is important for us to incorporate both of them in our model.

Perhaps, our naming and some lack of detail is to blame for some apparent confusion. Immortal time bias is indeed an important aspect of our study and needs to be addressed in the modeling. This is indeed why we use time-dependent covariates in the cause-specific hazard model. The “treatment” as mentioned above in our study is the exposure to medications (statins). The specific timing of this ‘treatment’ (when a patient starts taking a medication) occurs at different times in the follow-up for different patients. Hence, different patients will have different times for the ‘treatment’, therefore the impact of these different times need to be taken into account in the model to avoid immortal time bias, as you mentioned in your comment above. We modelled exposure to statins not as “categorical variable in variable ways” but precisely as to allow and account for the ‘treatment’ to occur at different times in the follow-up. The duration of statin intake along with when statin intake began (which is different for different patients) is very important to include when doing the analysis. Statin intake, or any other medication in our model is a time-dependant covariate, and that is how they are stored in the raw data. Hence, this is why we are using cause-specific hazard survival model with time-dependant covariates.

Now, as to why we called the statin covariate ever vs never, theoretically, a patient’s status can change not only from unexposed to exposed, but also from exposed to again unexposed, if he stops taking the statin. However, this rarely happened and we thought it would be better to handle the “treatment” as an intention to treat analysis and hence, if a patient was exposed to the statin at a particular time point, we coded all future time points also as exposed, but the previous time points all still remained as unexposed for the patient. Hence, making the exposure to statin variable a time-dependant variable. So even if a patient would be exposed at some time point he would still have previous time points where he would be unexposed. The “ever” means all future points going forward once exposed, and not the entire duration of the study which we see the word could incorrectly imply. Hence, you can clearly see that “treatment occurs at different times in the follow-up” as mentioned in the comment. Further, we also wanted to do a sensitivity analysis and wanted to see if adding a lag to the ‘treatment’ would improve the model. Hence, we created additional models with lags of 1 year, 3 years and 5 years. So the 1 year lag model would consider the ‘treatment’ to occur only when the patient had taken the statin for a complete year. Hence, causing the patients to be considered unexposed for the duration of the lag and exposed only after they had taken the statin for and entire year. Similarly, the 3 years and 5 years lag models were created. Due to these models we called the original model with no lag the ever vs. never model which you can see its ‘treatment’ is a time-dependent variable subject to immortal time bias. Now, when we did the sensitivity analysis we found the lags of 1 year, 3 years and 5 years to be statistically insignificant and dropped those models, however, we kept the name of the original model. Ever vs never simply meant no lag and the treatment being modelled as intention to treat.

Hence, to reiterate how we modelled statin use: statin exposure was defined as a time-dependent covariate; even though we talk about ever versus never exposure, this refers to exposure history up to particular time point. The ever vs never use of statins was defined at each point during the follow-up and used as a time-dependent covariate. Hence, at each point during the follow-up a patient can either be exposed or not exposed and his status can change from unexposed to exposed at any time point during the follow-up. This avoids immortal time bias that results from conditioning on future exposure information in survival analysis. To clarify this, we have reword the sentence "(ever vs. never exposure at any time point during the follow-up)" in the statistical analyses section as "(past ever vs. never exposure up to each time point during the follow-up)".

Lastly, to address the point that how is this different from regular Cox model, regular Cox model cannot handle time-dependent covariates. In regular Cox modelling, people need to be either categorized as exposed to statin or not exposed to statin from the beginning of the study. They cannot change from not exposed to unexposed. This difference is actually found in the structure of the data a, in fact, a lot of effort was put into having the correct structure so as to be able to model time-dependant covariates.

Moreover, I again suggest you to use logistic regression models for prediction of repeat biopsy and prostate cancer diagnosis. You still can treat the time of statin or other medications you did, but you would need to report odds ratios instead of hazard ratios. Indeed, you can treat both also as time to event outcomes, but then you need to report it also like this. Then you would need to report the median time to repeat biopsy/pca. diagnosis and how these changed due to statin or other medications intake. Because from a cox model you can only draw the conclusion that e.g. at 9 yrs or whatever timepoint, the risk to underwent repeat biopsy/been diagnosed with prostate cancer was lower in x vs y patients.

These were defined as time-to-event outcomes, time being the time for initial negative biopsy (beginning of study) to cancer diagnosis or repeat biopsy, to model their cause-specific hazard and thus cannot be accommodated by logistic regression. Even though it may appear the outcome is simply binary (prostate cancer diagnosed or not) the time it takes for an outcome to occur is meaningful, which logistic regression cannot take into account. For example, if all people in two different cohorts, getting two different treatments, get prostate cancer eventually, however, one cohort’s individuals take significantly longer (e.g. twice as long as the other cohort) logistic regression would consider the two cohorts the same. But as you can see the two are not, as one of the treatment is able to delay the negative outcome and is protective. This is because the time component of the time-to-event outcome is ignored in logistic regression, but is taken into account in survival models such as cox regression or cause-specific hazard model. Hence, logistic regression would not be correct to use.

Further, If the time component of these time-to-event outcomes are not taken into account and if it is also not taken into account that the exposure status of patients to the medications can change over the duration of the study (from not being exposed for a certain length of time and then being exposed for a certain length of time) there will be immortal-time bias. Both these aspects: (1) time-to-event outcomes and (2) time-dependant covariates, which is explained in detail in response to the first question, need to be handled and are taken into account by the cause-specific hazard modelling with time-dependant covariates. Logistic regression cannot handle either of these two issues, and will not be able to address immortal-time bias.

As for competing risks, the cause-specific hazard model is valid in the presence of competing risks, and is an alternative to the Fine & Gray model for the subdistribution hazard. We quote Austin et al. (Circulation 2016):

"Cause-specific hazard models can be fit in any statistical software package that permits estimation of the conventional Cox proportional hazards model. One simply treats those subjects who experience a competing event as being censored at the time of the occurrence of the competing event. In R, one can use the coxph function in the survival package, in SAS, one can use PROC PHREG, and in Stata, one can use the stcox function."

To clarify this, we have changed the term "Cox proportional hazard model", "Cox model" or "Cox-regression model" everywhere in the manuscript to "cause-specific hazard model".

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Hi,