Reviewer’s report

**Title:** Semi-parametric risk prediction models for recurrent cardiovascular events in the LIPID study

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**Reviewer:** Edsel A Pena

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1. A first event analysis is still valid, even if the event times for a subject are correlated; however, it is inefficient. So the statement that a first event analysis is not valid in several places in the manuscript need to be corrected.

2. There has been recent papers that appeared regarding the modeling and analysis of recurrent events which may be pertinent to the analysis of the LIPID data sets and which also shed some light on the complexities of analyzing recurrent events. For instance, the papers by Wang and Chang (JASA, 1999), Peña, Strawderman and Hollander (JASA, 2001), and Peña, Slate and Gonzalez (JSPI, 2007) provide discussions about the difficulties in analyzing recurrent event data. Perhaps the authors should look at these papers as well as others that have recently came out.

3. The application of models and statistical analysis for recurrent event (MI) data arising from the LIPID study is welcome and this data set could provide researchers a new set of data on which to test newly proposed analysis and perhaps perform comparisons of different methods. This manuscript is in this direction, aside from providing also scientific conclusions arising from the LIPID study.

4. This reviewer is actually somewhat concerned with the model considered in the analysis, which is equation (1). Let me explain. Let us denote by Sik the calendar time of the kth recurrence of MI for the ith subject, and let us denote by Ki the observed number of recurrences for this subject. The model used in the analysis is that Sik, given covariates Xi, has the hazard rate function given by

\[ h(k) \]

\[ (t | x_i) = h(k) \]
This modeling strategy is one form of the marginal modeling approach that has been used for dealing with recurrent event data. The other approach is the conditional approach, though the two models when viewed from a counting process perspective really only differ in the way the at-risk processes are defined. The model in (1) does not incorporate frailty, and somehow it does not also take into consideration the potential associations among the event occurrences for each subject. It is actually stated in the manuscript on page 6 that one of the virtues of this modeling approach is that it does need the specification of the dependence structure between the times of the recurrent events for each subject. Several issues though arise. The number of events observed for each subject, $K_i$, is actually informative about the recurrent event mechanism. This is better seen by letting $T_{i1}, T_{i2}, \ldots$ be the inter-event times among successive recurrences, i.e., $T_{ij} = S_{ij} - S_{ij-1}$. Even at the most extreme case of having no covariates and in which the $T_{ij}, j = 1, 2, \ldots$ are IID, say from $F$, observe that

$$K_i = \max k : S_{ik} = X_k$$

$$j=1$$

$$T_{ij} \cdot C_{ig};$$

where $C_i$ is the end of observation (or censoring) for the $i$th subject. That is, there is a constraint that the observed $S_{iks}$ or equivalently $T_{iks}$ must satisfy. It is also then immediately seen that $K_i$ has a distribution that depends on $F$. Where is this taken into account in this marginal method of analysis? Now, on the other hand, if you condition on the $K_i$ and $C_i$, then you know that each $S_{ik}, k = 1, 2, \ldots$; $K_i$ could not exceed $C_i$ and the distributions of the $S_{iks}$ are affected by this conditioning. A question is whether the model in (1) is still appropriate?

5. I am certainly aware of these marginal modeling methods of analysis (WLW; PWP; Therneau and Grambsch), but I believe that there are some very serious foundational issues that arise with the analysis of the recurrent event data that arise in this LIPID study because of the
data accrual system (the equation for $K_i$). I would like the authors to look into this and address them, or at the very least provide some discussions.

6. Other than these more foundational issues, the papers proceeds along the usual lines as outlined in Therneau and Grambsch and not much to comment about. I would point out however that there are also some conflicting interpretations of the results depending on the model utilized, and this also mirrors the foundational issues mentioned above. I believe that a more global model, instead of several marginal models, could do away with these conflicting interpretations.

7. Nevertheless, I welcome that more attention is being paid to a more appropriate approach to analyzing recurrent event data, and the data here could be another rich source of recurrent event data that statisticians could utilize in testing new models and methods.

8. I would therefore suggest to the authors including a richer set of references and a fuller discussion of some foundational issues, as I believe the are critical.

9. Minor: On page 9, "Same effect model".

10. Minor: On page 14, insert `be' before `related' on line -5.