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SHORT COMMUNICATION

The restricted mean survival time as a replacement for the hazard ratio and the number needed to treat in long-term studies

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Abstract

Background The restricted mean survival time (RMST) is increasingly being used as opposed to the hazard ratio (HR). In this framework, also the number needed to treat (NNT) needs to be placed in a specific methodological context.

Aims We applied the above mentioned parameters to analyse the survival data reported in the PARADIGM-HT trial that studied sacubitril + valsartan vs. enalapril in patients with heart failure. The estimates of these parameters were compared with one another.

Methods Two endpoints were evaluated: a composite of death or hospitalization and cardiovascular death. Our analyses were performed by considering the original follow-up of 41.4 months and on the basis of a lifetime perspective. All statistical calculations were carried out using specific packages developed under the R-platform.

Results According to our RMST analysis, the results for the composite endpoint in the comparison of sacubitril + valsartan vs. enalapril showed an improvement from 32.9 to 34.2 months (gain of 1.25 months). This result is based on a time horizon of 41.4 months. The results for the cardiovascular mortality endpoint showed a RMST of 37.2 months for sacubitril + valsartan vs. 36.2 for enalapril (gain of 0.96 months). In the two lifetime analyses, the improvements were much more relevant and yielded a gain of 25.8 months for the composite endpoint and 27.6 months for survival free from cardiovascular death.

Conclusions Using the data of the PARADIGM-HT trial, our analysis confirmed that the RMST has documented advantages over the HR, particularly when the clinical study is characterized by a long follow-up. The NNT has a more specific methodological role and cannot be replaced by the RMST.

Keywords Restricted mean survival time; Median; Hazard ratio; Number needed to treat

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Background

The literature on the restricted mean survival time (RMST) is growing very rapidly.1–8 In long term studies, the advantages of RMST over the hazard ratio (HR) and the number needed to treat (NNT) are well recognized, especially in oncology1,2,4 and in cardiovascular diseases.5–7

Briefly, the RMST does not differ too much from the well-known median, but has three important advantages: (i) the RMST is numerically much more stable than the median because it examines the whole survival curve, whereas the median examines the ‘exact’ time point in the curve when residual survival declines from >50% to <50%; (ii) unlike the median, the RMST takes into consideration also the portion of the survival curve that follows the achievement of the median (and therefore accounts for the presence of a survival plateau in the so-called ‘right tail’ of the curve, when this occurs); (iii) unlike the median, the RMST can handle the survival curves that, at the last time point of the follow-up, remain over 50% in residual survival.

Both HR and NNT are relative parameters and therefore have a comparative nature and they estimate if (and to what extent) the risk of an event changes from one treatment to another. In contrast, absolute parameters such as the RMST...
Results

Table 1: Characteristics of the two cohorts of the PARADIGM-HF trial and values of RMST, MST, NNT, and HR estimated from the time-to-event curves

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>RMST* (mos) with 95%CI</th>
<th>MST (mos) with 95%CI</th>
<th>At 36 mos</th>
<th>At 60 mos</th>
<th>HR* with 95%CI</th>
<th>Survival gain (mos) with 95%CI</th>
</tr>
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<tbody>
<tr>
<td>Composite of death or hospitalization</td>
<td>Enalapril</td>
<td>3,023</td>
<td>34.2 (22.3 to 39.5)</td>
<td>106.3 (105.0 to 107.5)</td>
<td>19</td>
<td>14</td>
<td>0.82 (0.73 to 0.89)</td>
<td>2.25 (1.3 to 3.2)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Sacubitril + valsartan</td>
<td>4187</td>
<td>34.2 (22.3 to 39.5)</td>
<td>106.3 (105.0 to 107.5)</td>
<td>19</td>
<td>14</td>
<td>0.82 (0.73 to 0.89)</td>
<td>2.25 (1.3 to 3.2)</td>
</tr>
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</table>

CI, confidence interval; HR, hazard ratio; mos, months; MST, mean survival time; N, not computable; NNT, number needed to treat; RMST, restricted mean survival time; *t*, milestone.

*All values of RMST refer to a time horizon of 41.4 months (i.e., t* = 1260 days).

The values of HR are drawn from McMurray et al.

The survival gain according to medians could not be computed because the median was not reached in either arm.

The two main endpoints are reported.
Reanalysis of the PARADIGM-HF trial

vs. enalapril showed an improvement from 32.9 to 34.2 months (a gain of 1.25 months). It should be kept in mind that this information refers to a time horizon restricted to 41.4 years. In the paper by Srivastava et al.,8 the values of NNT for the composite endpoint were estimated to be 19 and 14 at 3 and 5 years, respectively.

The results for the cardiovascular mortality endpoint showed a RMST of 37.2 months for sacubitril + valsartan vs. 36.2 for enalapril (a gain of 0.96 months). The corresponding values of NNT for cardiovascular mortality7 were 27 and 19, respectively.

As regards the two lifetime analyses (Table 1), the improvements were much more relevant, yielding a gain of 25.8 months for the composite endpoint and of 27.6 months for survival free from cardiovascular death.

Finally, the values of HR determined in the original trial were 0.80 for both endpoints. The trial evaluated the efficacy of sacubitril + valsartan over enalapril, and there was no placebo arm; the putative placebo effect ascribed by Srivastava et al.8 was obtained from indirect analyses.

Conclusions

Our main result is that the values of RMST are much easier to interpret than those of NNT and HR.

In fact, from the perspective of the individual patient, the prognosis suggested by the NNT provides no practical information. On the other hand, the technical usefulness of the NNT remains undisputed from the perspective of the treating physician. In addition, the NNT is relevant at the population level to inform patients about the potential effectiveness of a drug.

In our RMST analysis, the incremental benefit at 41.4 months for sacubitril + valsartan vs. enalapril (gain of 1.25 months for the composite endpoint; 0.96 months for cardiovascular mortality) showed a limited magnitude. In contrast, the lifetime incremental benefit expressed through the RMST gave a much more relevant difference (gain of 25.8 months for the composite endpoint; 27.6 months for cardiovascular mortality). As regards the comparison between RMST (or MST) vs. HR, the values of RMST and MST clearly showed that the incremental benefit of the new treatment accumulates mainly on the long-term, and so an assumption is needed that the difference in favour of the new treatment remains stable beyond the follow-up length reached in the clinical study (proportional hazard assumption). This assumption holds also in the case of HR, but in our view, it remains too implicit in the case of HR, whereas both RMST and MST explain this point much more explicitly.

In conclusion, the evolving literature about the use of RMST in cardiovascular diseases9,10 deserves an increasing attention because some traditional parameters used as a standard for many decades are likely to be replaced, at least in part, by the RMST, particularly as regards long-term studies.

To completely remove the HR is unrealistic, but stressing its main disadvantages may be useful because the HR continues to be used very widely with little awareness of its limits. In contrast, the proposal of abandoning the NNT in survival statistics cannot be recommended despite some limitations of this parameter. Finally, it should be stressed that the results presented herein are in keeping with those published in a recent article by Ferreira et al.13

Authors’ contribution

The three authors contributed equally to this study.

Conflict of interests

None declared.

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