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 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 27.5 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

Received: 23 July 2020; Revised: 3 January 2021; Accepted: 2 March 2021
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Background

The literature on the restricted mean survival time (RMST) is growing very rapidly.¹⁻³ 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 oncology,¹⁻⁴ 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

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and the median do not directly determine the risk of a negative event, but simply indicate the event-free life expectancy that can be attributed to the patient. Patients understand more easily the concept of the length of an expected event-free survival (e.g. expressed in months per patient); the same thing does not occur with the HR or the NNT, that are ‘pure’ numbers, that is dimensionless parameters, and, more importantly, only exist in the context of a comparison.

The literature on the new treatments for patients with heart failure and reduced ejection fraction (e.g. angiotensin receptor-nephrin inhibitors and inhibitors of sodium–glucose cotransporter 2) offers some useful examples on the advantages of RMST. 5–7

Aims

Our analysis was aimed at determining the values of RMST from the survival curves for sacubitril + valsartan vs. enalapril reported in the PARADIGM-HF trial. 8 Furthermore, the values of RMST were compared with those of HR and NNT.

Methods

To determine the RMST for sacubitril + valsartan vs. enalapril from the PARADIGM-HF trial, we used the RMST software as implemented in the R platform. 9,10 This method estimates the RMST with its 95% confidence interval (‘survRM2’ package) and allows for a lifetime extrapolation according to the Weibull function (‘eha’ package); this extrapolation generates a mean lifetime survival (MST). 11 To perform these analyses, the graphs of the Kaplan–Meier curves 12 were digitized as previously described 13; individual patient data were reconstructed from the Kaplan–Meier curves. 14

To ensure that the RMSTs calculated from the different curves were comparable, the follow-up time was restricted (‘truncated’) for all curves at 1260 days (or 4.14 months), which was the maximum time value reported in the Kaplan–Meier graphs. The endpoints for these analyses included a composite of death or hospitalization and cardiovascular mortality. Furthermore, our results were compared with those reported by Srivastava and co-workers. 8

Results

Table 1 shows the comparison between our results based on the RMST and those of Srivastava and co-workers 9 based on the NNT.

According to our RMST analysis, the results for the composite endpoint in the comparison of sacubitril + valsartan
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., 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 mortality 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 effi-
cacy of sacubitril + valsartan over enalapril, and there was
no placebo arm; the putative placebo effect reported by
Srivastava et al. 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 infor-
mation. 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 payers 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 MST 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 be-
between RMST (or MST) vs. HR, the values of RMST and MST
clearly showed that the incremental benefit of the new treat-
ment accumulates mainly on the long-term, and so an as-
sumption 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 assum-
ption). 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 diseases deserves an increasing at-
tention because some traditional parameters used as a stan-
dard 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 can be useful because the HR continues
to be used very largely with little awareness of its limits. In
contrast, the proposal of abandoning the NNT in survival sta-
tistics 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 re-
cent article by Ferreira et al.

Authors’ contribution

The three authors contributed equally to this study.

Conflict of interests

None declared.

Funding

This paper was not funded.

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<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>RMST&lt;sup&gt;a&lt;/sup&gt; (mos) with 95%CI</th>
<th>Lifetime MST (mos) with 95%CI</th>
<th>NNT At 36 mos</th>
<th>NNT At 60 mos</th>
<th>HR&lt;sup&gt;b&lt;/sup&gt; with 95%CI</th>
<th>Survival gain (mos) with 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death or hospitalization</td>
<td>Sacubitril + valsartan</td>
<td>4187</td>
<td>34.2 (33.8 to 34.6)</td>
<td>105.1 (100.6 to 109.9)</td>
<td>19</td>
<td>14</td>
<td>0.80 (0.73 to 0.87)</td>
<td>1.25 (1.17 to 1.34)</td>
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<tr>
<td></td>
<td>Enalapril</td>
<td>4212</td>
<td>32.9 (32.5 to 33.3)</td>
<td>79.4 (76.7 to 82.1)</td>
<td></td>
<td></td>
<td></td>
<td>25.8 (23.2 to 28.4)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NC</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Sacubitril + valsartan</td>
<td>See above</td>
<td>37.2 (36.8 to 37.5)</td>
<td>154.8 (145.0 to 165.2)</td>
<td>27</td>
<td>19</td>
<td>0.80 (0.71 to 0.89)</td>
<td>0.96 (0.81 to 1.14)</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>See above</td>
<td>36.2 (35.9 to 36.6)</td>
<td>127.2 (120.6 to 134.1)</td>
<td></td>
<td></td>
<td></td>
<td>27.6 (24.9 to 30.3)</td>
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<td>NC</td>
</tr>
</tbody>
</table>

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

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

<sup>b</sup> The values of HR are drawn from McMurray et al.12

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.