

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

Aims We applied the restricted mean survival time (RMST) to analyse the survival data reported in the PARADIGM-HT trial in which sacubitril + valsartan was studied in comparison with enalapril in patients with heart failure. The estimates of this parameter were compared with the published values of hazard ratio (HR).

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 number needed to treat (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 oncology^{1,2,4} 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 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-neprilysin 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 curves¹² were digitized as previously described¹⁰; individual patient data were reconstructed from the Kaplan–Meier curves.¹⁰

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 41.4 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-workers⁸ based on the NNT.

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 (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

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

Endpoint	Treatment	No. of patients	RMST ^a (mos) with 95%CI	Lifetime MST (mos) with 95%CI	NNT		Survival gain (mos) with 95%CI	
					At 36 mos	At 60 mos	From RMST ^a	From life-time MST
Composite of death or hospitalization	Sacubitril + valsartan	4187	34.2 (33.8 to 34.6)	105.1 (100.6 to 109.9)	19	14	1.25	25.8
	Enalapril	4212	32.9 (32.5 to 33.3)	79.4 (76.7 to 82.1)			0.80 (0.73 to 0.87)	NC ^c
Cardiovascular death	Sacubitril + valsartan	See above	37.2 (36.8 to 37.5)	154.8 (145.0 to 165.2)	27	19	0.96	27.6
	Enalapril	See above	36.2 (35.9 to 36.6)	127.2 (120.6 to 134.1)			0.80 (0.71 to 0.89)	NC ^c

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.

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

^bThe values of HR are drawn from McMurray *et al.*¹²

^cThe survival gain according to medians could not be computed because the median was not reached in either arm. The two main endpoints are reported.

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 mortality⁸ 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.¹² The trial evaluated the efficacy of sacubitril + valsartan over enalapril, and there was no placebo arm; the putative placebo effect reported 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 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 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 the difference in favour of the new treatment is assumed to remain stable beyond the follow-up length reached in the clinical study (proportional hazard assumption beyond follow-up). This assumption holds also in the case of HR, but in our view, it remains too implicit in the case of HR, whereas MST explains this point much more explicitly.

In conclusion, the evolving literature about the use of RMST in cardiovascular diseases^{5–7} deserves an increasing attention because some traditional parameters used as a standard for many decades (especially the HR) 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 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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