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Review Article

Outcomes at 5 years in patients with severe aortic stenosis: reviewing current information using the restricted mean survival time

Andrea Messori, Laura Bartoli, Sabrina Trippoli

HTA Unit, Toscana Region Health Service, Toscana Region, Florence, Italy

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Abstract: The information about outcomes at 5 years in patients receiving transcatheter aortic valve replacement (TAVR) has grown. We interpreted the information on this topic using the restricted mean survival time (RMST). The purpose of our study was to summarise the current evidence using an original outcome measure with potential methodological advantages. Four cohorts of patients, previously published in the literature, met our criterion of 5 years of follow-up after the implant; another cohort was identified from a group of controls subjected to surgical replacement of the valve. The estimated values of RMST at 5 years for the 5 patient cohorts were the following (N = number of patients, all time values in years): a) real-world high surgical risk cohort: N = 114, RMST = 3.80; b) real-world cohort treated with Corevalve: N = 309, RMST = 3.79; c) a real-world cohort treated with Sapien: N = 180, RMST = 3.61; d) TAVR arm of a randomized trial in intermediate risk patients: N = 1,011; RMST = 3.73; e) surgical replacement arm of the same trial: N = 1,021, RMST = 3.72. The main result of our analysis based on the RMST is represented by the extreme homogeneity of the outcomes (RMSTs ranging from 3.61 to 3.80 years per patient) that remained virtually constant irrespective of the baseline risk of the patients (intermediate or high risk) and regardless of whether the intervention was transcatheter or by surgical replacement. Last but not least, our analysis showed the good methodological performance of the RMST in this disease condition.

Keywords: TAVR, restricted mean survival time, Kaplan-Meier, network meta-analysis

Introduction

Although the restricted mean survival time (RMST) is considered a new methodological tool for interpreting time-to-event curves, its development dates back to almost 20 years ago. In comparison with the median, the RMST has an advantage because it examines the whole survival curve (as the hazard ratio) and expresses the survival outcomes on a scale of time (as medians). More importantly, the RMST can be determined from any survival curve whereas the median cannot be computed when less than 50% of the patients have experienced the event.

Previous experiences in the application of RMST are mostly focused on oncology [1], but other areas are being investigated as well [2, 3]. Re-examining the current evidence on a given therapeutic topic using the RMST rather than traditional outcome measures (i.e. the hazard ratio and the median) is worthwhile because the RMST provides estimates of effectiveness that can differ from those based on traditional metrics. When these differences occur (see for example reference [4]), there is a quite universal agreement that the analysis based on the RMST is more reliable than the "traditional" analysis. In 2019 or 2020, each of 8 major international journals (New England Journal of Medicine [5], Lancet [6], Journal of Clinical Oncology [7, 8], Annals of Internal Medicine [9, 10], Annals of Oncology [11], Circulation [12], Journal of the American College of Cardiology [13], and Journal of the National Comprehensive Cancer Network [14]) have published at least one methodological paper that emphasized the advantages of the RMST in comparison with traditional outcome measures such as the hazard ratio. Overall, during the

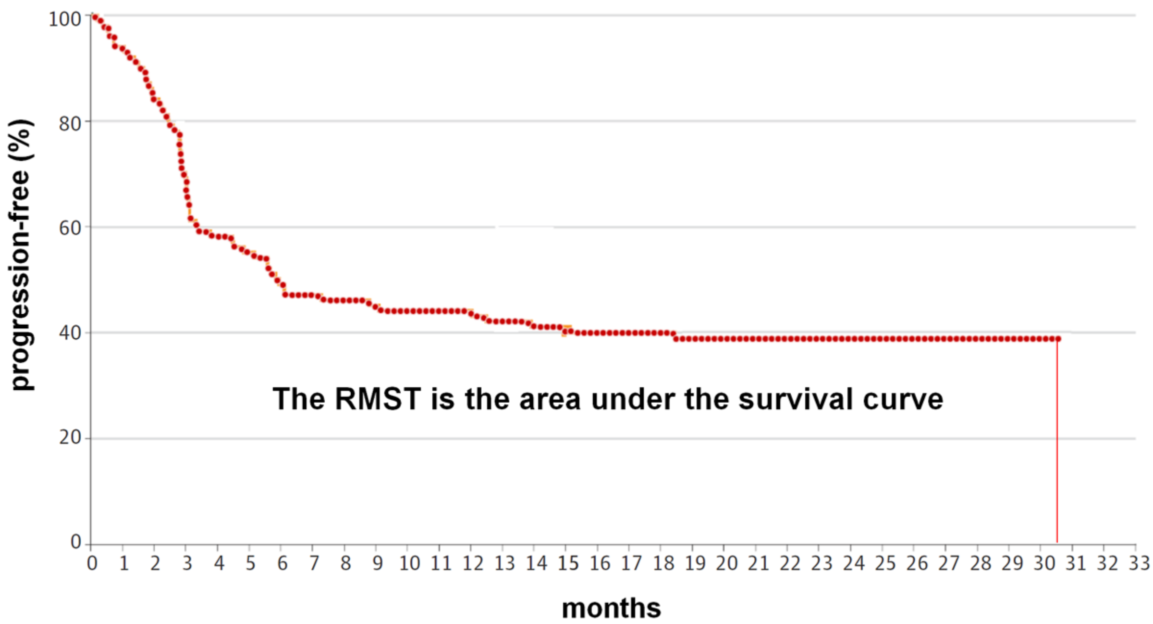

Figure 1. In the analysis of a Kaplan-Meier curve the RMST is represented by the area under the curve. This progression-free curve refers to 108 patients with B-cell lymphoma treated with a CAR-T (axicabtagene ciloleucel). See reference 18 for further details.

past 12 months PubMed has indexed a total of 55 articles that dealt with the RMST [15].

As regards the application of the RMST in practice, an original model-independent method of calculation, drawn from the field of pharmacokinetics, has simplified the otherwise complex estimation of RMST [16, 17]. In more detail, the model-independent approach employs the so-called trapezoidal rule (commonly used in pharmacokinetics) to estimate the area under the survival curve, the value of which corresponds to the RMST (**Figure 1**). In the analysis described below, we assessed the RMST at 5 years in 5 patient cohorts with severe aortic stenosis recently published in the literature [19-21]. These cohorts were treated with surgical replacement of the valve or with trans-catheter aortic valve replacement (TAVR).

Patients with severe aortic stenosis: analysis of the current evidence

The present analysis was aimed at applying the RMST to the cohorts of patients with severe aortic stenosis included in observational or experimental studies published thus far. We selected only the studies characterized by a follow-up of at least 5 years. In the original studies describing these cohorts [6-8], the composite end point of disabling stroke or death was evaluated according to a standard time-to-event statistics (Kaplan-Meier).

We reassessed this clinical material to determine the values of RMST for each curve according to model-independent methods. A total of 5 cohorts were analysed. These cohorts consisted of a real-world high operative risk cohort (n = 114) [19], another real-world cohort treated with Medtronic Corevalve (n = 309) or Edwards Sapien (n = 180) [20], and a randomized trial comparing TAVR (n = 1011) versus surgical replacement (n = 1021) in intermediate-risk patients [21].

The model-independent values of RMST were determined according to the area under the curve (AUC) calculation previously described [16, 17]. This model-independent method employs the commonly used trapezoidal rule for estimating the value of AUC, which directly represents the estimate of the RMST. Each curve was truncated ("restricted") at the last time point in the follow-up ("milestone" or t*). Hence, t* was set at 5 years. An exception was made for the curve by Ichibori et al. [19] (follow-up = 8 yrs) that was "truncated" at 5 years to ensure comparability with the other curves.

Table 1. Characteristics of the five cohorts, values of RMST, and ranking of the treatments examined in our analysis

Rank	Data set	No. of patients	Milestone (t*) (years)	RMST (years) with 95% confidence interval
1§	Real-world high surgical risk cohort treated with any TAVR (curve truncated at 5 yrs) [6]	114	5	3.80 (3.63 to 3.98) SEM: 0.089316
2	Real-world cohort treated with Medtronic Corevalve [7]	309	5	3.79 (3.69 to 3.90) SEM: 0.054330
3	Real-world cohort treated with Edwards Sapien [7]	180	5	3.61 (3.46 to 3.75) SEM: 0.074678
4	TAVR arm of the randomized trial in intermediate risk patients [8]	1,011	5	3.73 (3.67 to 3.79) SEM: 0.030620
5	Surgical replacement arm of the randomized trial in intermediate risk patients [8]	1,021	5	3.72 (3.66 to 3.78) SEM: 0.030548

§ In a separate analysis with t* = 8 yrs, the analysis of this curve gave a RMST of 5.18 years (95% CI, 4.94 to 5.43; SEM: 0.126515). Abbreviations: RMST, restricted mean survival time; yrs, years; t*, milestone; SEM, standard error of the mean.

The 95% confidence intervals (CIs) for RMST were calculated as previously described [22]. According to this approach, the equations for determining the 95% CI of a proportion are applied to the ratio of event-free AUC vs total AUC, where total AUC is defined as the number of patients multiplied by t*. The statistical significance in pairwise comparisons was determined by standard unpaired t-test [23]. Statistical significance was set at 0.05. Ethical approval and patient informed consent were not needed because our study was a re-analysis of results already published in the literature [19-21].

Ranking of the treatments according to RMST values

The 5 cohorts were ranked according to the respective values of RMST. It should be noted that this non-parametric approach of elementary ranking resembles the one commonly employed in network meta-analysis [24]. A total of 5 separate RMST analyses were performed (**Table 1**). The graphs of the 5 fitted curves are shown in **Figure 2**. The values of AUC of these fitted curves generated the corresponding values of RMST.

Overall, these values of RMST (**Table 1**) provide an original summary of the outcomes at 5 years expected from TAVRs and from surgery. **Table 1** shows also the results of our ranking analysis. One important result is given by the extreme homogeneity of the 5 RMSTs (range: from 3.61 to 3.80 years) that remained virtually constant irrespective of the baseline risk of the patients (intermediate or high risk) and regardless of whether the intervention was transcatheter or by surgical replacement. Finally, since the RMST values for the 5 cohorts were nearly identical with one another (**Table 1**), the rankings showed no practical interest (with the partial exception of the difference in favor of Corevalve vs Sapien; see below).

Direct and indirect pairwise comparisons

In the direct comparison between Sapien and Corevalve [20], a numerical difference in favor of Corevalve was found, that remained around the limits of statistical significance (P = 0.049 which is not perfectly in line with the P = 0.15 originally calculated by the authors). In the comparison between TAVR and surgery based on the trial by Makkar et al. [21], the outcomes were nearly identical for TAVR (3.73 yrs) vs surgery (3.72 yrs), and no statistics was performed (P = 0.21 according to the original study).

We performed also an indirect comparison between high risk patients and intermediate risk patients, both given TAVR. Quite unexpectedly, the numerical results were in favor of high-risk patients (3.80 yrs vs 3.73 years at 5 years, respectively), but the difference was far from significance despite the large number of patients (P = 0.47).

Discussion

The main objective of this paper was to offer a comprehensive overview of the outcomes expected at 5 years in patients with severe aortic stenosis. The main strength of our analysis is related to the methodological choice in favor

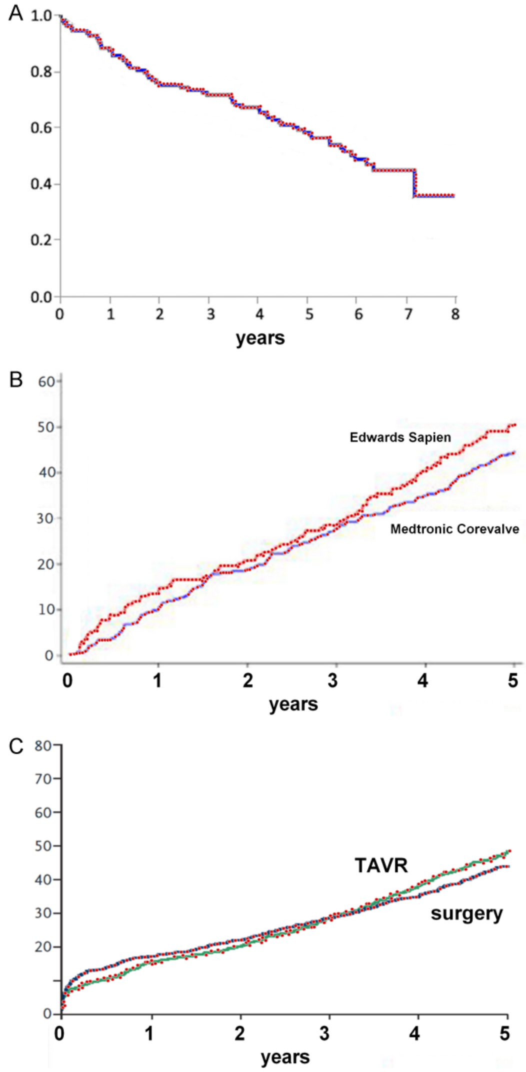

Figure 2. Five Kaplan-Meier curves of patients with aortic stenosis were included in our analysis. For each individual curve, the survival curve fitting procedure generated the small red circles that, in the three panels, are superimposed to the original curves as published in the respective articles. According to these red circles, (A) (real-world cohort with follow-up at 8 years), (B) (patients treated with Edwards Sapien or Medtronic Corevalve), and (C) (real-word TAVR versus surgery) show the computer-generated curves based on their respective x-vs-y data pairs. As regards the 4 curves shown in (B and C), the values of cumulative incidence were firstly converted from time without event into time to event; then, in analyzing the 5 curves, the AUCs were estimated from these x-vs-y data pairs by application of the trapezoidal rule. In the model-independent approach, RMST is known to be identical to AUC. Panel (A) shows the survival curve along with its 95% CI. In all Panels, time is expressed in years. Y-axis shows event-free survival (A) or cumulative event rate (B and C).

of the RMST, which is an outcome measure devoid of the typical disadvantages of the median and the hazard ratio [1-15]. The applicability of the RMST has no exceptions in the field of time-to-event curves. In contrast, the median is not computable when only a few events have occurred and survival remains above 50%. Another advantage of the RMST is that it is an absolute parameter and, also, is determined on a scale of time; in contrast, the hazard ratio is a relative parameter represented by a dimensionless number, which is difficult to be explained to the patients; furthermore, a HR makes sense only in the context of a comparison. Last but not least, the RMST does not require any access to the data-base of individual patients since the material of the study is the published graph of the Kaplan-Meier curves; likewise, no advanced statistical software is necessary to run the RMST procedure. Apart from these essential points, the comparison of the advantages and disadvantages of RMST vs median and hazard ratio is a complex issue on which we make reference to the excellent literature published on this topic [1-15].

Considering these methodological advantages, our finding that outcomes in this disease condition are virtually identical irrespective of the surgical or transcatheter replacement approach and of the intermediate or high surgical risk of the patient is remarkable because no such findings had previously been reported.

The presence of a ranking within our RMST procedure is a characteristic in common with network meta-analysis [24]. In the comparison between a strategy of multiple RMST estimations vs the typical strategy of network meta-analyses based on the hazard ratio, one point of controversy is that survival meta-analyses generally disregard the length of the follow-up. On the other hand, medians are technically unsuitable for inclusion in a standard meta-analysis (e.g. because in many cases they are not computable) and anyhow they miss the right tails of the survival curves. In contrast, in the RMST-based procedure the length of the follow-up is given the attention that it deserves. In this context, the unexpected strong homogeneity of the results of our analysis confirms the already known conservativeness of the RMST and suggests that the statistical significance of some hazard ratios previously reported in these patients should be interpreted with caution.

In conclusion, the current scenario of treatments for aortic valve stenosis is rapidly evolving. Our paper has pursued the objective to confirm the basic evidence concerning the outcomes of these patients, but, more importantly, has identified an original framework for studying effectiveness in this specific clinical setting according to the RMST.

Disclosure of conflict of interest

LB is recipient of a post-doctoral scholarship awarded by the Regione Toscana; AM and ST declare no conflicts of interest.

Address correspondence to: Dr. Andrea Messori, HTA Unit, Regional Health Service, Regione Toscana, Via Alderotti 26/N, 50135 Firenze, Italy. Tel: +39-338-9513583; E-mail: andrea.messori.it@gmail.com; andrea.messori@regione.toscana.it

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