What industry taught us about repeated time-related events

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A positive aspect of the first recall of the Braunwald-Cutter heart valve for catastrophic poppet escape was assistance from industry regarding how to assess rare device failures. General Electric statistician Wayne Nelson, PhD, was particularly helpful in introducing us to analysis of repeated¹ and weighted events²: repeated repairs of electric motors and cost of those repairs in his experience. Buried in General Electric technical reports, his methods were independently discovered by Aalen.³

Unlike medicine, which focuses on survival, industry focuses on the hazard function—the instantaneous risk of events. Constant hazard means “random failure”; high initial hazard means “burn-in.” The hazard function, however, is inherently noisy. The area under the hazard curve—cumulative hazard—mitigates this noise. Nelson’s major contribution was devising a nonparametric (non-model-based) method to estimate cumulative hazard $\Lambda(t)$. Raw data are the number of events (usually 1) at time k (n_{dk}) and the number of subjects (such as motors) at risk at that time (n_{rk}). Cumulative hazard at any time t_i is the sum of the ratios n_{dk}/n_{rk} up to that time:

$$\Lambda(t_i) = \sum_{k=1}^i \frac{n_{dk}}{n_{rk}}$$

Importantly, the number at risk is not decreased at an event’s occurrence. It remains the same until a subject dies, follow-up ends, or the subject is no longer at risk (eg, has had a faulty valve replaced).

For a terminating event, such as death, the Nelson and Kaplan-Meier estimates converge to the same answer (see Appendix 1), because $\Lambda(t_i) = -\ln[S(t_i)]$, where $S(t_i)$ is survival at time t_i . The Kaplan-Meier method, however, which is based on probability, is limited to a single terminating event. Nelson’s method has no such limitation, allowing patients—like motors—to remain under observation as subsequent events of the same nature are observed. Further, the event does not have to be binary (yes/no); it can have a value (such as cost, length of stay,⁴ or degree of severity of the event).

Repeated reinterventions after neonatal repair of critical aortic stenosis.

Central Message

Investigations often analyze only the first occurrence of a sequentially repeating time-related event. All these events can be analyzed, providing superior power for statistical and clinical inferences.

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The unit of cumulative hazard is events/patient. If events are infrequent, one might graph cumulative hazard as events per 100 or per 1000 patients. Similarly, cumulative cost yields quantity per patient, but this can be multiplied for quantity per 100 or 1000 patients.

But that is not all! Kalbfleisch and Prentice⁵ introduced us to the industrial method of “modulated renewal,” embodied in terms such as “good as new,” “better than new,” and

FIGURE 1. Repeated reinterventions after neonatal repair of critical aortic stenosis,⁶ illustrating modulated renewal analysis. The darkest curve is freedom from a first reintervention. Those experiencing a first reintervention are restarted at time zero, and the second curve is freedom from a second reintervention after having experienced a first reintervention, and so forth. Notice that after each reintervention, the likelihood of having another intervention progressively diminishes. This adds yet another dimension to clinical inferences beyond that of the Nelson repeated-events method.

“worse than new.” One simply uses the Kaplan-Meier method to depict time to first event from time zero. Then, individuals experiencing the first event are started at that new time zero, and a Kaplan-Meier curve is drawn to depict freedom from a second event. This is repeated for each subgroup of patients experiencing recurrence of the event. Both the Nelson and modulated renewal methods have been applied to congenital heart disease (Figure 1).^{6,7}

As we reviewed the original manuscript of Balasubramanya and colleagues' article⁸ on right ventricular outflow tract reintervention after primary tetralogy of Fallot repair in this issue of the *Journal*, we believed they could perform a more powerful analysis using these methods that accounted for repeating events (events being the effective sample size for time-related analyses⁹). They⁸ took our advice and analyzed these repeated reinterventions, resulting in greater insight into their nature after repair of tetralogy of Fallot.

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APPENDIX 1. COMPARISON OF KAPLAN-MEIER AND NELSON ESTIMATORS

The Kaplan-Meier estimator for survival at time t_i , $S(t_i)$, is as follows:

$$S(t_i) = \prod_{k=1}^i \left(1 - \frac{n_{dk}}{n_{rk}} \right),$$

where n_{dk} is the number of terminating events at time t_k , n_{rk} is the number remaining at risk, and Π means to multiply the k th term by the preceding product.

Cumulative hazard is the negative natural logarithm ($\ln$) of $S(t_i)$ (remembering that logarithms turn products into sums), where Σ means to add the k th term to the preceding sum:

$$A(t_i) = \sum_{k=1}^i \ln \left(1 - \frac{n_{dk}}{n_{rk}} \right).$$

To convince you that $\ln(1 - n_{dk}/n_{rk})$ is nearly the same as n_{dk}/n_{rk} , which Nelson's method uses, if $n_{rk} = 100$ and $n_{dk} = 1$, then $1 - n_{dk}/n_{rk} = 0.99$, and its natural logarithm is 0.01005. Compare this with the Nelson estimate of $n_{dk}/n_{rk} = 1/100 = 0.01$. For all practical purposes, they are equivalent (and much easier to calculate than using logarithms!).