Misinterpretation of time-to-first event curves can lead to inappropriate treatment

To the Editor:

Great care should be taken when assessing the consistency of treatment effect over time based on a survival curve plot, and even more so when a treatment affects a repeating event end-point, such as exacerbations, rather than an event that can occur only once, like death.

In their recent editorial in the *European Respiratory Journal*, Suissa and Ariel [1] make the assertion that survival functions plotted from Kaplan–Meier estimates from figure 1b in the IMPACT study [2] "clearly show that the difference in the rate of exacerbation between LAMA/LABA/ICS and LAMA/LABA over follow-up is due to the first month's surge, with practically no differences in the subsequent rates between the two groups". However, this statement is based on a misunderstanding of the survival analyses presented.

The events plotted on the figure are the *first* moderate or severe COPD exacerbations experienced by a patient in the IMPACT study. The statements made by Suissa and Ariel [1] about exacerbation rates refer to the rate of *first* exacerbations only, and not to the rate of all exacerbations during the study.

Their conclusion that the rates of *first* exacerbations, and ratio between those rates changes over time is correct. However, this is entirely in line with statistical theory for repeated events with overall constant rates. It cannot be used to support any conclusion that the difference in the rate of exacerbation is due to a "first month's surge". The "digitised" curve of first events behaves entirely consistently with constant rate events. Drawing any conclusions about the durability of the treatment effect on *all* exacerbations from this digitised plot, which shows only first exacerbations, is methodologically incorrect.

Consider a repeating event end-point (such as exacerbations) in two treatment groups, A (low constant rate) and B (high constant rate). Initially the gradient of the survival curve for the *first* event for treatment B (high rate) will be very steep, because all patients are "at risk" of an event. As fewer and fewer patients are left available to have a first event, the gradient will necessarily diminish. The gradient of the survival curve for the *first* event for treatment A (low rate) will eventually become steeper. Eventually the two survival curves for time to *first* event will converge despite event rates being different in both arms, as illustrated in the figure, which is described by the equations below.

Suppose that in treatment arm A events occur at a constant annual rate of 1.0, and in treatment arm B events occur with a constant annual rate of 1.5. The exponential survival functions (*i.e.* the functions that describe survival for events with constant hazard rates) are given by:

$$S^{\text{Treatment } A}(t) = 1 - \exp(-\text{t})$$

$$S^{\text{Treatment } B}(t) = 1 - \exp(-1.5\text{t})$$

where t is the time in years [3]. The resulting survival curves can be plotted and it is also possible to differentiate with respect to t, to obtain the gradient $G(t) = \text{S}'(\text{t})$ of the survival curves, which corresponds

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Evaluation of treatment effect durability over time cannot be based on analyses that examine the first of many events. Here, it is explained how misinterpretation of survival curves led to wrong conclusions in a recent *ERJ* editorial. http://bit.ly/2K3amgQ

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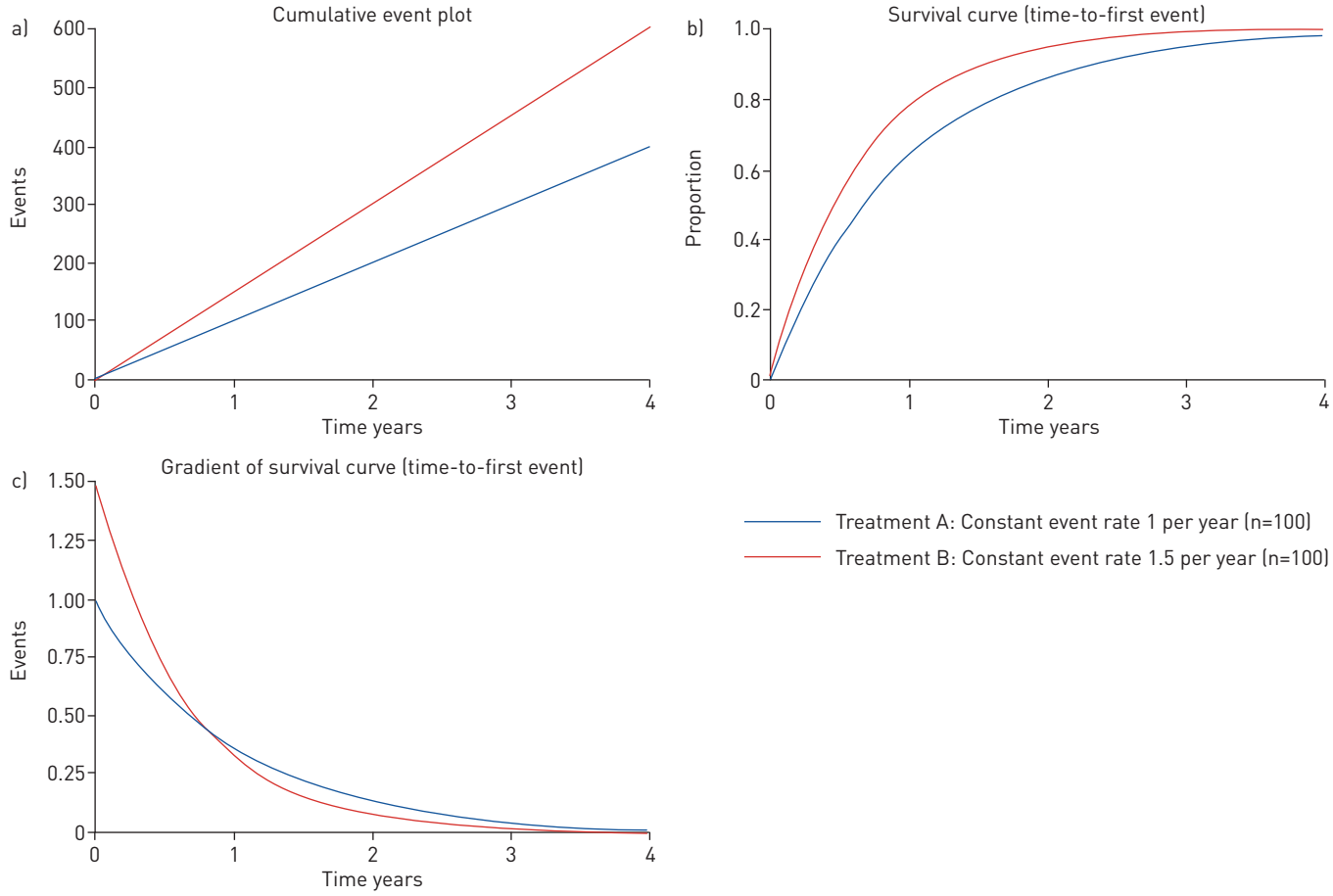

FIGURE 1 Hypothetical example of a cumulative event plot, survival curve and gradient of survival curve presented on the same data.

to the digitised plot presented by Suissa and Ariel [1].

$$G^{\text{Treatment } A}(t) = \exp(-\text{t})$$

$$G^{\text{Treatment } B}(t) = 1.5\exp(-1.5\text{t})$$

These survival curves converge, and the gradient of both curves start to diminish, with the gradient functions crossing exactly as shown in the real data (figure 1). It is important to understand this phenomenon occurs for constant rate events, and therefore its presence should not be taken as evidence that the rates are not constant.

This can be understood in the following way: the cumulative incidence or survival curve only describes the first event experienced by each patient. If treatment A consistently reduces the rate of events, then these first events will be delayed but they will still occur. While patients on treatment A are experiencing their first events there are simply fewer patients on the treatment B arm who are still "at risk" of a first event, these events having already occurred. By this point patients on treatment B are having second or third events, which are not captured by a time to first event analysis, thus the rate of their first events has diminished.

This illustrates that conclusions about the durability of the treatment effect over time cannot be based on analyses restricted to looking at only the first event of many. To imply that the treatment effect diminishes because one survival curve catches up with another is inappropriate and risks propagating incorrect information, which could lead to harm to patients if treatment is withdrawn or not used.

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From the authors:

We thank B. Hartley and co-workers for their correspondence on our analysis of the IMPACT triple therapy trial [1]. We welcome this opportunity to correct some misunderstanding of the computation of monthly rates of exacerbation, when converted from the cumulative incidence curve, as applied to the IMPACT trial.

The rate of a first exacerbation for a given month of follow-up is based not only on the gradient of the survival function as the numerator, as understood by B. Hartley and co-workers, but must also include the survival function as the denominator denoting the subjects at risk of an exacerbation [2]. Thus, the monthly rate is approximated by the difference between the cumulative incidence value at the end of each month with that at the beginning of that month, divided by the survival at the beginning of the month. Using the notation of B. Hartley and co-workers (somewhat confusing since S(t) is typically used to denote the survival function, not the cumulative incidence function as employed in their correspondence), the "rate" at a given point in time (hazard function) is:

$$h(t) = G(t)/(1 - S(t)).$$

The corresponding average rate over a given time interval t_1 to t_2 is given by:

$$\text{rate} = (S(t_2) - S(t_1))/((t_2 - t_1)(1 - S(t_1))).$$

This is the monthly rate of exacerbation displayed in our figure for the long-acting muscarinic antagonist (LAMA)–long-acting β-agonist (LABA) and triple therapy groups, approximated from the cumulative incidence curves, for the IMPACT trial [1]. It clearly shows that the first month's surge in the rate of exacerbation in the LAMA–LABA group is real, with no differences in the subsequent rates between the two groups during the following 11 months. Thus, contrary to the claim of B. Hartley and co-workers, this proper calculation of the rate supports the conclusion that the difference in the rate of exacerbation between the two groups is due to the first month's surge.

This pattern of an early surge, known as "depletion of susceptibles", can be informative to understand a treatment's effect [3]. This sudden surge is not unexpected in the IMPACT trial with the abrupt withdrawal of inhaled corticosteroids (ICS) imposed at randomisation and its inclusion of a patient

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The IMPACT trial of triple therapy in COPD confirms that benefit on exacerbations is only in first month with no benefit in following 11 months, likely due to inclusion of asthma-like patients, suggesting a precision medicine opportunity in COPD treatment http://bit.ly/2YxQpH0

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population with a history of asthma, over-represented by frequent exacerbators with milder airflow limitation [4].

Rather than this mathematical sophistication, it would have been more straightforward and certainly more informative if B. Hartley and the authors of the IMPACT trial had simply provided estimates for these monthly rates of an exacerbation directly from the trial data available to them. The authors could then confirm the surge with the actual trial data, and also investigate the role of prior ICS use that was abruptly discontinued at randomisation, as well as prior asthma diagnosis, frequent exacerbator phenotype, GOLD stage and eosinophilia, on this surge. Such analyses would provide valuable data for a better precision medicine targeting of the right treatment for the right patient [5]. Most importantly, this would also allow to prevent unnecessary harms from ICS to those patients who would not benefit from triple therapy.

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