Time T—to understand treatment response

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In personalised medicine, understanding treatment effect heterogeneity in randomised controlled trials is essential. Comparing subgroups with better and worse treatment responses can reveal characteristics or pathways that differentiate responders from non-responders.

In the field of obstructive lung diseases, interventions targeting exacerbations often use total event rates as the primary outcome. However, as this outcome averages the number of events across all participants, whether a treatment effect is broadly distributed over the studied population or driven by specific subgroups remains indiscernible.

Time-to-first-event analyses are valuable complementary outcomes, as equal weight is assigned to all participants in reaching the studied outcome. Although participants are censored after their first event, the timing of first events and pattern of time-to-first-event curves can provide key insights into response dynamics. Since exacerbations are the best predictors of future events, patients with a short time to their first event are—on a group level—at an increased risk of also experiencing subsequent exacerbations at shorter intervals.[1,2] Meaningful assumptions can be made based on this simple idea, particularly if time-to-first-event curves cease to diverge during follow-up.

We propose a framework in which integrating both analyses can help to better understand treatment responses for recurrent event rates and potentially identify treatable traits. The total event rate curve, represented by the cumulative mean number of events, reveals the nature and sustainability of treatment responses (figure). Only when the curves for treated and untreated groups continue to diverge does the treatment have a sustained effect, at least during the time of the follow-up (figure, A). If the curves become parallel or reconverge (figure, B and C), the treatment delays early events in the treated group, but without affecting the overall rate of subsequent events, which might warrant a reassessment of the value of the intervention.

Integrating cumulative total event rates with the time-to-first-event curves offers a more nuanced understanding of the dynamics underlying overall treatment effects. Steadily diverging total event rate curves might be assumed to correlate with continuous divergence in time-to-first-event curves throughout follow-up (figure, A with D), however, this is not always the case. Time-to-first event curves might stop diverging or even begin to reconverge at a specific timepoint (timepoint T), which corresponds to a depletion of susceptibles phenomenon. Initially, a steeper incline in incidence of first events is expected in control patients, as their high-risk profile remains untreated. However, as fewer susceptible patients remain at risk, the probability of events will decrease and curves will cease to diverge from treated patients.[3] Meanwhile, total event rate curves might continue to widen beyond T if the treatment maintains an effect on recurrent events (figure, A with E, or A with F).

The NOTUS trial,[4] which investigated dupilumab for preventing chronic obstructive pulmonary disease (COPD) exacerbations, can be a good example of these changes. Over 52 weeks, the mean exacerbation rate was 0·86 in the dupilumab group versus 1·30 in the placebo group (rate ratio 0·66; p<0·001). Early in the trial, time-to-first-event curves diverged between treated and untreated groups. However, by week 16, divergence ceased, and the difference remained constant for the remainder of the 52-week follow-up. Nevertheless, the cumulative mean total event rate curves continued to diverge steadily, indicating that the treatment effect was further driven by a reduction of recurrent events.[3]

Plotting the cumulative incidence of first events (which is not completely similar to time-to-first-event) alongside the total event rate curve, reveals additional insights (figure, H–I). First, the ratio of the red to blue area approximates the rate ratio driven by recurrent events, with a smaller ratio indicating a stronger treatment effect on recurrent events. Second, timepoint T—if identified in the time-to-first-event curves—marks the point beyond which further divergence in total event rates is driven solely by treatment effects in patients who already had at least one event. Therefore, the earlier T appears in the trial, the more likely the overall intervention effect will be driven by recurrent event reduction. Assuming first and recurrent events share similar pathophysiological mechanisms, an early T should prompt subgroup analyses, as the observed effects might be driven by smaller subgroups that strongly express the pathways

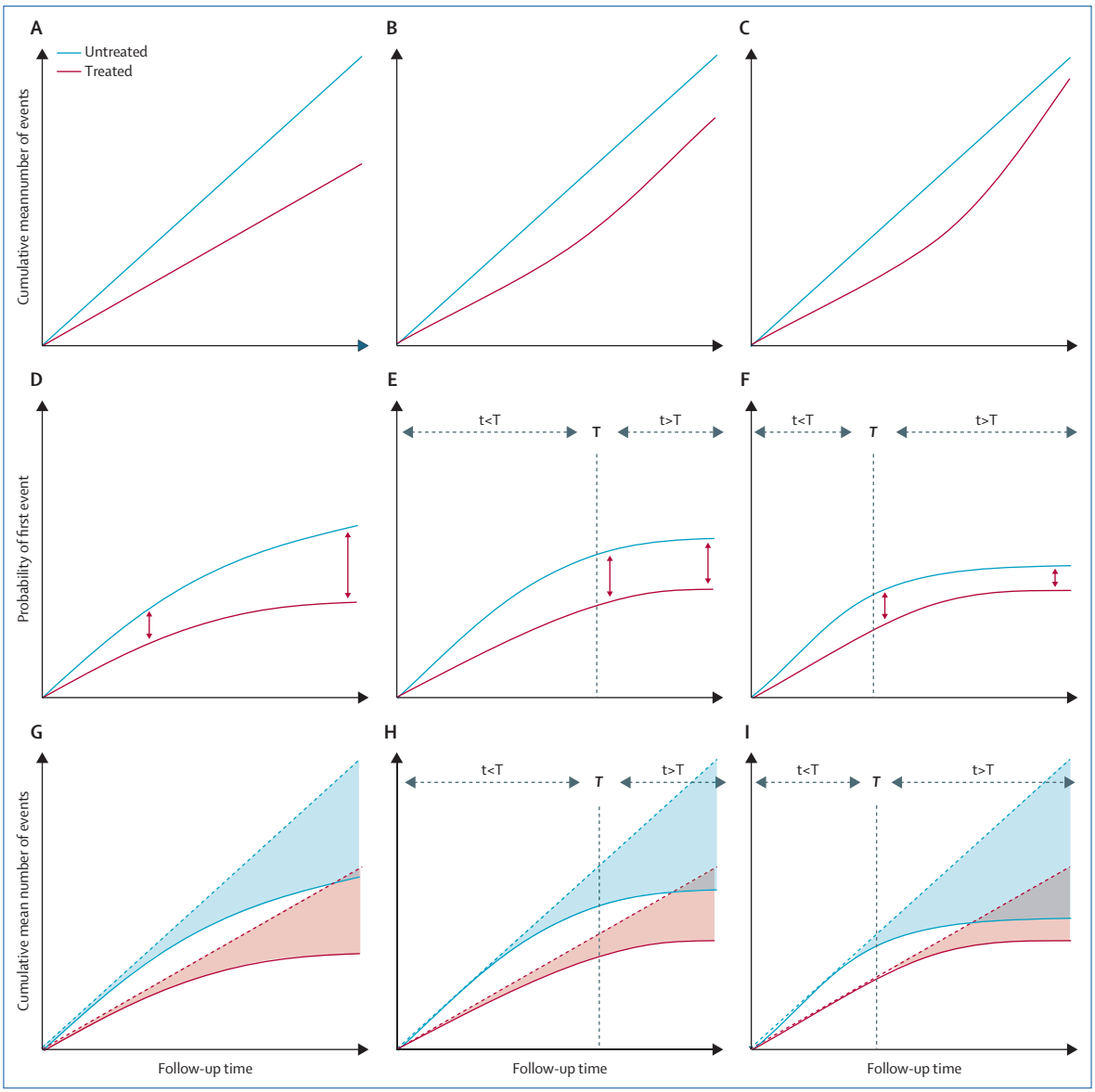

Figure: **First and total events over time**
Different scenarios for cumulative mean number of total event curves (A, B, and C), time-to-first-event curves (Kaplan Meier estimate; D, E, and F), and combined cumulative number of first and total event curves (G, H, and I) of intervention (red) and control (blue) arms of a randomised controlled trial. Total event rates might keep diverging throughout a trial (A *vs* B or C), whereas time-to-first-event curves cease diverging or reconverge at timepoint T (A and D *vs* A and E or F). The red over blue area ratio approaches the cumulative treatment effect on recurrent events. Early occurrence of T (F or I) suggests the intervention effect is primarily driven by recurrent event reduction.

targeted by the treatment.[5,6] We expect that for the NOTUS trial, people with higher baseline concentrations of fractional exhaled nitric oxide (FeNO; >20 ppb) benefitted most from dupilumab both on primary and recurrent events.[7]

Timepoint T might also mark a transition for the risk of an event. In the placebo arm, patients with an event before T (t<T) probably have a higher risk profile than individuals with their first event after T (t>T; respectively 22% vs 20% of patients in NOTUS, with T at 16 weeks). Individuals who had no events during the trial presumably have the lowest baseline risk (58% in NOTUS). Comparison of baseline characteristics of T-defined subgroups could indirectly identify descriptors for both the observed treatment effect and event risk. In fact, if such traits are present (eg, high FeNO), one would expect them to be more prevalent in the t<T placebo group as compared with the t>T placebo group, in which

a treatment effect on first event is no longer observed. Similarly, the prevalence of such traits should be lower in the t<T treated group compared with the t<T placebo group, as the treatment shifts patients with these traits beyond T.

In conclusion, total event rate curves might keep diverging throughout a trial, whereas time-to-first-event curves show only small differences and cease diverging at a timepoint T. Identifying T might provide important insights into treatment effects on recurrent events and characteristics of patient subgroups, which drive event risk but also treatment effects.

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