The Power of More Than One

Paul W. Armstrong, MD; Cynthia M. Westerhout, PhD

There is widespread recognition of the increasing challenge of conducting adequately powered clinical trials in cardiovascular medicine. Given the broadening gap between guideline-based recommendations and the level of evidence supported by trials, this matter is a central priority. Two fundamental properties characterize the contemporary assessment of cardiovascular clinical trials. First, they are generally designed to evaluate the time to first event between the study arms. Second, different clinical events, presumed to be related to the targeted disease of interest, are commonly combined to form a composite end point. This approach increases the number of events observed during follow-up, usually but not always enhancing the statistical power and efficiency of clinical trials (ie, reducing the number of patients required).

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Despite these established analytic techniques, several potential liabilities exist. The first event within a composite end point may not reflect the most clinically important or relevant one. Thus, incorporating subsequent events seems rational to provide a more comprehensive perspective of disease burden or therapeutic efficacy. This would also be timely, given that the recognition of recurrent events has emerged as a matter of increasing interest to patients, healthcare providers, and payers. The interpretation of composite end points can be perplexing, particularly when the directions of the individual components differ.

In this issue of Circulation, Kohli et al address recurrent multiple events in the recent Platelet Inhibition and Patient Outcomes (PLATO) trial. The PLATO trial definitively demonstrated a treatment benefit of ticagrelor compared with clopidogrel in the primary end point of vascular death, myocardial infarction (MI), or stroke across a broad spectrum of patients with acute coronary syndromes. The authors provide evidence indicating that ticagrelor reduces the occurrence of not only first events but also subsequent cardiovascular events. It should be appreciated, however, that the large majority (ie, 83%) of the overall treatment effect of ticagrelor on the primary composite end point was expressed on the first event. In contrast, there was only a modest and nonsignificant additional advantage of ticagrelor (Figure 1A in the Kohli et al article, intergroup absolute difference; n=16 events; \( P=0.40 \)) on the recurrence of the 3 components of the composite. Although a post hoc assessment of all-cause mortality coupled with time to the second event showed a reduced hazard ratio in favor of ticagrelor, there was substantial overlap in the 95% confidence intervals (second event or death: hazard ratio, 0.80; 95% confidence interval, 0.70–0.90; first event: hazard ratio, 0.84; 95% confidence interval, 0.77–0.92).

The Figure illustrates 3 possible patient experiences over the course of the study that complicate the analysis of multiple recurrent events. As shown in case 1, early vascular death precludes a recurrent event. In case 2, however, an MI is followed by a complicating embolic stroke leading to death, highlighting the likelihood of dependence, not independence, of recurrent events. Statistical methods for multiple recurrent events, including the Wei-Lin-Weissfeld approach used in the present report, generally assume independence among events; however, this method has provisions to account for dependencies between events (ie, marginal analyses for time to the first, second…kth event; robust sandwich covariance matrix). Finally, in case 3, the length of follow-up is curtailed because of late entry into the trial. Because PLATO was an event-driven trial, the overall duration of study treatment was <12 months for many patients, and the total duration of follow-up was as short as 6 to 9 months in some patients, thereby abbreviating their opportunity for a recurrent event. Because the hazard of first versus subsequent events is modulated in part by length of follow-up, it would be useful to further explore the impact of this issue.

Although the present report suggests that the lack of a difference between ticagrelor and clopidogrel in recurrent bleeding “could not be attributed to higher rate of discontinuation,” this seems at odds with a prior PLATO report on bleeding complications that indicates a significant discontinuation of study medication after nonprocedural bleeding between treatments (ie, first bleed: 2.4% ticagrelor versus 1.0% clopidogrel, \( P<0.001 \); absolute: 224 versus 95 events, respectively). Interestingly, although this major bleeding (ie, not related to the procedure or to coronary artery bypass graft surgery) was similar between treatment groups before 30 days, it increased with ticagrelor after 30 days (3.1% versus 2.3%; \( P<0.05 \)). This pattern highlights the complexity of deciding whether to continue therapy when an event occurs that could be related to the disease of interest on the one hand or the therapeutic intervention on the other. Whereas dual antiplatelet therapy is associated with a continuing hazard, the risk of a recurrent event after the index event may diminish over time (as is the case in many patients with acute coronary syndromes). Hence, insightful clinical judgment using appropriate models to assess relative risks is required. Given the spectrum of acute coronary syndrome patients represented in PLATO and the likely differences in recurrent events among those with unstable angina,
non-ST-segment-elevation MI, and ST-elevation-elevation MI, it would be useful to know the impact of these 3 subsets on the results of the present report.5,8

To optimally understand the clinical applicability of the findings of Kohli et al, it is useful to consider them in the context of individual patients. Hence, of the 1888 patients experiencing a primary end point, we learn that 318 patients experienced at least 2 events and further presume an additional 76 patients had at least 3 events. Although we do not know the sequencing or texture of these events, we can surmise that a large MI with heart failure versus a small periprocedural MI or a disabling nonfatal hemorrhagic stroke versus a transient left arm weakness would have dramatically different consequences on patient care. Therein lies the rub when we homogenize clinical events such as MI and stroke. We can, and should, do a better job of classifying these events into prognostically relevant categories.9

Understanding the relative importance of components of a composite has been the subject of work both within and beyond cardiovascular medicine.1,10,11 Recently, an approach that “weights” the components of a clinical trial, according to a consensus acquired by a Delphi panel of clinical investigators, demonstrated how this method can better inform its interpretation and provide greater precision around end-point estimates.3,12

Kohli et al, like others previously, have provided welcome attention to the potential power of counting >1 event per patient in a clinical trial.4,13–15 This stimulates us to propose a strategy to enhance the conduct of future clinical trials in cardiovascular medicine (Table).16–18

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**References**


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<th>Table. A Proposed Strategy for Future Clinical Trials in Cardiovascular Medicine</th>
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<td><strong>Record all patient events, not just the initial event, and report as per-patient and overall rates.</strong></td>
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<td><strong>Prespecify the use of common clinical event definitions to permit intertrial comparisons, including a gradation of event severity (eg, for stroke: transient ischemic attack, transient minor disability, and severe permanent disability).</strong></td>
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<td><strong>Establish consensus on the relative clinical significance of differing clinical end points and prespecify to derive a weighted score for each patient.</strong></td>
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<td><strong>Disseminate and use statistical methods for recurrent multiple events used in other arenas (eg, AIDS).</strong></td>
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<td><strong>Further engage regulators and journal editors in the process of systematically reporting procedures.</strong></td>
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