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EDITORIAL

Classification of Deaths in Cardiovascular Outcomes Trials

Known Unknowns and Unknown Unknowns

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In 2002, Donald Rumsfeld, then US Secretary of Defense, famously stated "There are known knowns. There are things we know that we know. There are known unknowns. That is to say, there are things that we now know we don't know. But there are also unknown unknowns."[1] His comment captures the range of possibilities when information is uncertain; from knowable to unknowable. Also, in science, it is the unknown unknowns that present the greatest challenge.

Randomized, controlled, blinded clinical trials remain the gold standard for evaluating efficacy and safety of new therapeutics. Their primary strength is the elimination of any potential bias in the comparison between the investigational treatment(s) and control(s). However, as for any experiment, the methods of conduct of the experiment affect the quality of the science and the ability to achieve an adequate test of the hypothesis as intended. In the case of clinical outcomes trials, this important principle plays out through trial operations, which inherently influence the science and the robustness of the experiment. In our experience, countless operational decisions in the conduct of a clinical trial affect the quality of the experiment. Considering 1 important domain, many clinical trials use clinical event committees (CECs) to provide consistent assessment (adjudication) of clinical outcomes based on trial specific definitions. In this issue of *Circulation*, Fanaroff and colleagues[2] present new analyses elucidating variability in the rates of adjudicated, undetermined cause of death and provide an important example of this interaction between trial operations and the output of the experiment.

WHY WAS THIS RESEARCH CONDUCTED?

In most registration-pathway cardiovascular outcomes trials, central CEC adjudicators who are unaware of treatment assignments (blinded) categorize the cause of deaths. For each death, the CEC attempts to separate cardiovascular deaths from noncardiovascular deaths. This adjudication process enables investigators to examine cardiovascular deaths and composite end points that include cardiovascular death (rather than all deaths). All-cause mortality, which aggregates cardiovascular deaths and noncardiovascular deaths, is free of any potential subjectivity in classification, is clinically compelling and is most relevant to patients. However, noncardiovascular deaths (eg, death from lung cancer) may not be influenced by a therapy directed at a specific cardiovascular pathophysiology. Because we favor specificity in efficacy end points as providing the highest fidelity determination of the cardiovascular effect of a therapy, we believe that the use of composites using cardiovascular death is best practice for the primary efficacy analysis in most cardiovascular outcomes trials. This effort is of heightened importance in trials designed to test cardiovascular safety or

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noninferiority of a therapy, because inclusion of events that are not expected to be differentially affected by the experimental therapy will potentially obscure any difference between treatments and lead to a false conclusion. Therefore, in the ideal circumstance all deaths are accurately classified as cardiovascular or noncardiovascular.

However, during adjudication, in cases in which it is not possible to discern the cause of death, the CEC may categorize the death as undetermined. A task force established by the United States Food and Drug Administration recognized this actuality but had the expectation that such undetermined deaths "should be very few… and rare in well-run clinical trials."[3] Until now, however, no structured effort to describe the proportion and correlates of undetermined deaths had been undertaken.

WHAT DID THE RESEARCHERS FIND?

Fanaroff and colleagues[2] interrogated trial-level and patient-level data for 9259 deaths from 9 clinical trials across a spectrum of cardiometabolic disease (acute coronary syndromes, stable atherosclerotic vascular disease, diabetes mellitus, and atrial fibrillation). Seven of the trials were from a single academic research organization. Adjudication classified 15.6% of deaths as undetermined (range 7.0% to 21.7%) compared with 13.2% of deaths characterized as undetermined by the site investigator. The proportion of adjudicated undetermined deaths varied by therapeutic area, stable atherosclerosis being highest (20%) and acute coronary syndrome the lowest (12.5%). However, with only 9 trials included, we advise caution in interpreting variability by therapeutic area and by year of publication, because these data from trial-level analysis may be driven by specific standard operating procedures of individual trials rather than the variables of interest. For example, if a single trial in a therapeutic area systematically made less robust efforts to seek documentation, it would appear (erroneously) that the proportion of undetermined deaths would be related to that therapeutic area. Regional variation in the proportion of undetermined deaths suggested by the patient-level analyses is more credible. This finding is also plausible because completeness of follow up and the availability and robustness of documentation may differ by region. The higher rate in North America (17.2%) compared with other regions of the world,, however, is not well explained by this study. Patient-level analyses also revealed associations between older age or a longer interval from randomization to death with a higher likelihood of an undetermined death.

In the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial, adjudicators were asked to prospectively record whether the source documents available were sufficient to determine the cause of death (ie, whether the cause of death was unclear despite complete information being provided versus that the records provided were insufficient because of missing information). Remarkably, 94.3% of undetermined deaths were classified by the adjudicator as having "limited or no source documents."[2]

INTERPRETATION AND IMPLICATIONS

Our overarching interpretation of these findings is that the operational components of clinical outcomes trials matter. The observed associations with time from initial randomization and regional variation suggest that the extent to which contact is maintained with the subject and accessibility of records have important influence. In our experience, the ability to adjudicate the cause of a death as cardiovascular or noncardiovascular is dependent on (1) the quality and completeness of the records provided to the adjudication committee, (2) the threshold for completeness that is expected by a CEC to render a decision (related to training and precedent), (3) the persistence of the committee to seek and obtain documents that are likely to be present but have not been submitted, and (4) the temporal relatedness of the death to an acute event that qualified the patient for the trial (Figure). In trials of patients with acute myocar-

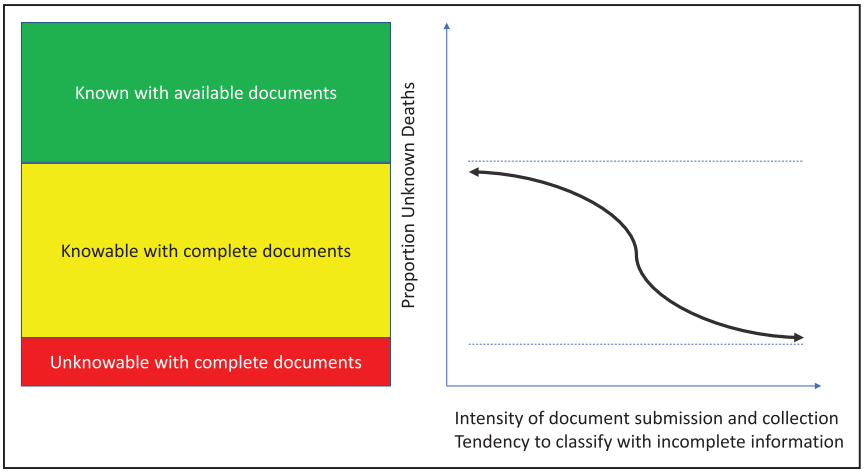

Figure. Classification of cause of death in clinical trials and the influence of document collection and willingness to classify with some uncertainty.

dial infarction, for example, deaths early in follow-up are more likely to be reasonably deemed as cardiovascular in cause than those that occur many years later during follow-up or in trials of chronic stable cardiovascular conditions in which the competing risk of a noncardiovascular death is higher in relative terms. However, the doggedness with which medical records are pursued is likely more important than these temporal relationships.

In general, an undetermined cause of death may be related to (1) missing or insufficient documents in which the cause of death could have been known with complete documentation, (2) clinical circumstances in which the cause may be unknowable (eg, a subject who lives alone and is found dead after an uncertain duration and has no autopsy), or (3) when a subject limits study personnel from obtaining complete data (eg, withdrawal of consent for follow-up). Depending on the proportions of these underlying reasons, the number of undetermined deaths will differ under different operational systems. Collection of these reasons for classification as undetermined cause of death during adjudication in future trials may be informative for assessing the quality of data, and to guide future research and improvement in these processes.

The success of efforts to determine the unknown is supported by clarity in expectation of complete reporting by investigators and the depth and extent of documentation required. For example, complete documentation such as an admission and discharge summary for a hospitalized patient is more likely to provide clarity than a death certificate.[4] Collection of complete data is facilitated by a trial infrastructure designed to support collection of information that enables the local investigators to maintain contact with the subjects or their caregivers, the expectations that investigators are held to by the trial leadership in pursuing medical records for deceased patients, and the number of patients who withdraw consent or are lost to follow-up, in whom often only limited registry information regarding vital status is available. This perspective, informed by our experience, is supported quantitatively by the striking proportion of cases in Fanaroff et al's analysis of undetermined deaths for which adjudicators reported incomplete medical records.

Fanaroff et al's data provide a range of observed rates of undetermined deaths (7.0% to 21.7%) among trials adjudicated predominantly by 1 research group, as well as reported rates for 10 external trials (2.0% to 26.8%). It is not possible to determine from the data presented whether there is an optimal rate. If the authors were able to determine the rate of undetermined deaths in subjects with complete documentation, this would be a better assessment of a benchmark proportion. We note that of 19 trials, only 3 had a proportion of undetermined deaths that was <5% and that 11 had a proportion >10%. Moreover, it is conceivable that the trials that had very low rates had processes in which adjudicators defaulted to cardiovascular or noncardiovascular deaths in circumstances in which another committee may not have rendered such an opinion (ie, adjudicated as unknown) with questionably sufficient records. Nonetheless, a proportion <10% appears achievable with the assiduous effort that we have described.

These new data from Fanaroff et al suggest that undetermined cause of deaths in cardiovascular outcomes trials are not rare. Nevertheless, it should be the goal of adjudication committees to maximize information, minimize uncertainty, and limit our use of unknown classifications to those deaths for which the cause is unknowable.

ARTICLE INFORMATION

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