Nonfatal Myocardial Infarction Is, by Itself, an Inappropriate End Point in Clinical Trials in Cardiology

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In a number of double-blinded, clinical trials in cardiology,1-4 the occurrence of a nonfatal myocardial infarction has served as a secondary end point and, in at least one,5 as the primary end point. We believe that this practice may be inappropriate. An assumption underlying the separate analysis of nonfatal infarction is that there may be pathophysiological differences between fatal and nonfatal infarctions so that the effect of treatment on one of these outcomes may be different from the effect of treatment on the other. However, the difference between a fatal and a nonfatal myocardial infarction is often the result of chance factors (e.g., having an ambulance called immediately after the ischemic attack, being brought to a hospital where first-rate coronary intensive care is offered), not of biological ones.

Under a competing assumption that the difference between a fatal and a nonfatal infarction is mainly a matter of severity, inferences about the effect of treatment on nonfatal infarctions may be ambiguous. For example, a reduction in the incidence of nonfatal infarction could represent a harmful effect if the intervention has no effect on the overall incidence of infarctions but increases their severity so that more infarctions are fatal. On the other hand, a reduction in the incidence of nonfatal infarction could represent a beneficial effect if the intervention reduces the overall incidence of infarctions without necessarily affecting those that are fatal. These conflicting possibilities suggest that when there is research interest in nonfatal infarctions, they should be analyzed in tandem with fatal infarctions and not by themselves. If a group of patients experience a reduction in the incidence of nonfatal infarctions, it must be ascertained that the reduction was not at the expense of an increase in the incidence of fatal events.

A problem exists in the statistical analysis of nonfatal infarctions. Consider a clinical trial in which patients who have survived a myocardial infarction are randomized to receive one of two treatments. Each patient is followed until study termination, loss to follow-up, or the occurrence of the study’s end point, whichever comes first. If the end point under consideration is a new nonfatal myocardial infarction, patients who die before experiencing it are censored at the time of death; they are included in the analysis as alive and at risk of experiencing the end point until that time and are then withdrawn from the analysis.

Available methods of survival analysis assume that a patient who experiences a censoring event is at the same risk of subsequently experiencing the end point (nonfatal reinfarction) as a prognostically similar patient who survives as long but is not censored.6 This may be an appropriate assumption for deaths due to causes such as cancer or cirrhosis of the liver, but it is likely to be erroneous for sudden deaths. In one study,7 two thirds of postinfarction patients who died within 24 hours of the onset of symptoms were found on autopsy to have suffered a new myocardial infarction. The assumption concerning the independence between censoring and experiencing the study’s end point is completely erroneous, finally, when deaths due to a documented new myocardial infarction are censored.

A practical reason for considering nonfatal infarctions alone as an end point is that information is frequently lacking to classify a death as being due to a definite new myocardial infarction. In contrast, a patient whose infarct is nonfatal has the opportunity to report the clinical symptoms and to undergo the laboratory and electrocardiographic tests required for diagnosis. Some deaths, however, occur late enough after the patient’s arrival in the hospital to permit a diagnosis of definite myocardial infarction.

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Rather than censor these cases, it is more sensible to count them as occurrences of a slightly broadened end point, definite myocardial infarction, whether fatal or not. This suggestion is consistent with standard practice in clinical trials in neurology: nonfatal stroke seems never to be analyzed as a separate end point but is instead combined with fatal stroke.

Other deaths due to coronary heart disease, especially those that occur soon after the onset of ischemic symptoms but without detailed medical information, may or may not be due to a myocardial infarction. Caution suggests that these cases be analyzed twice, once by censoring them and once by counting them along with the definite infarctions as occurrences of a yet broader end point, definite or probable myocardial infarction, whether fatal or not.

We suggest that in trials aimed at testing whether an experimental agent reduces the risk of myocardial infarction, the primary end point be a definite infarction, fatal or not, and that a secondary end point be a definite or probable infarction, fatal or not. An alternative primary end point that is in wide use is the composite event defined as a nonfatal myocardial infarction or death due to coronary heart disease, whichever occurred first. This end point is referred to as “coronary incidence,” “coronary heart disease event,” and “first recurrent cardiac event.”

Nonfatal myocardial infarction should not be used by itself as an end point. After all, it is the infarction that one is seeking to prevent, not just the nonfatal one.

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References

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