Does It Matter Why and How Patients With Heart Failure Die? 
A Debate That Lives On

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Our interest in death and illness is nothing but a way of expressing an interest in life” —Thomas Mann, The Magic Mountain.

Is the retort to the declarative statement that “dead is dead” now dead? Simply answered, not at all. In the heart failure discipline, whether data are derived from clinical trials, registries, or epidemiological studies, delineating “why” and “how” patients die remains a keen interest for investigators. Cross-reference “cause of death” with “heart failure” in an online publication database, and you will find almost 60 papers in the 10 years since the “dead is dead” issue was raised. Why are we so engaged in this task? Perhaps it is because the underlying goals are sound: to understand the impact of interventions according to treatment assignment and to better understand the pathophysiology and natural history of heart failure.

We have in fact learned a great deal from a long list of studies: For example, patients with nonischemic cardiomyopathy can die of ischemic complications, implantable defibrillators may shift death from a sudden arrhythmic cause to progressive heart failure, and sudden death is clustered in the early period after myocardial infarction. Such analyses can also raise interesting hypotheses or help to demonstrate the robustness of a treatment effect, as, for example, when an intervention reduces both sudden and nonsudden causes of death. Many of these concepts apply not only to death as an end point but to any number of other cardiovascular events, such as stroke or nonfatal myocardial infarction.

We also know that there are implicit limitations in all such studies, which are based in part on the lack of availability of comprehensive and relevant clinical data and on the definitions themselves. Long the purview of clinical trial events committees, these definitions may not be “user friendly” across clinical trials or be easily translated for use in large epidemiological databases. Even the simplest classification schema, such as arrhythmic death versus circulatory failure, can be criticized because of overlap and difficulties recreating the events that lead to death. Indeed, the fact that necropsy findings often do not correlate with “best estimates” from clinical data, including medical records, leads to even more uncertainty about whether we are really measuring what we think we are measuring. In addition, when it comes to categorizing a death, arguments can reach almost philosophical levels. What constitutes an arrhythmic death? Can a death be sudden if the patient has severe functional limitations and leads a New York Heart Association class IV existence? What does it mean if a drug or intervention causes a redistribution among the various causes of death without meaningfully affecting overall death rates?

Now, in the present issue of Circulation: Heart Failure, Henkel and colleagues come into the fray, using data from Olmsted County, Minn, to examine the causes of death in a community cohort with incident heart failure between 1979 and 2002. Great effort was expended to ascertain whether death occurred; the sample is also unusual in that death certificates were completed in the majority of cases by a medical examiner or Mayo Clinic pathologist. Of particular note, death due to noncardiovascular causes increased with time from diagnosis and was more likely among patients with preserved rather than reduced ejection fraction (49% versus 36%). Interestingly, one of the lessons appears to be that although quantitative differences existed between the 2 groups, noncardiovascular causes were remarkably common regardless of ejection fraction, and thus, it appears reasonable to posit that there is a need to address comorbidities to a greater degree than previously appreciated.

Despite these provocative findings, the naysayers can maintain that nothing has fundamentally changed, because we should be thinking more about how patients die than about cause. Indeed, it may be that we have not spent enough time finding out what death with advanced heart failure actually looks like.

If that is the case, should we continue to explore the cause of death in heart failure? A reasonable argument can be made that we must first establish some uniformity of definitions, even while acknowledging the artificiality of such an exercise, at the very least to facilitate study-to-study comparisons. This may allow for some unexpected benefits, including modification of risk-stratification models that currently predict all-cause death. Second and most importantly, if we gain better insight into what patients want or expect from chronic illness, we can certainly justify further study. While doing so, we should avoid the temptation in clinical trials and...
registries to examine the cause of death in small subgroups, especially if they are not prespecified. Furthermore, analyses should have meaning beyond the fulfillment of a regulatory requirement. Patients (and their physicians who care for them) should know more about what to expect as heart failure progresses and how various therapeutic options can affect not only the duration and quality of life but the quality of death as well. Therefore, “why” and “how” patients with heart failure die matter, not only to us on a macroscopic level but almost certainly to the patients who live with heart failure but may or may not die of it.

Disclosures

None.

References

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