
Keeping Apples and Oranges Separate: Reassessing Clinical Trials That Use Composite End Points as Their Primary Outcome

It has become increasingly common for clinical trials in cardiovascular medicine to use composite primary end points that often have varying clinical importance. Time-to-event analyses, in which mortality is but one of several outcomes, are particularly problematic as the impact of death is clearly not equivalent to other nonfatal outcomes such as rehospitalization (1). Another concern is that indiscriminately combining mortality with other outcomes in survival analyses may lead to biases related to “competing risk” (2). Specifically, patients dying early in a clinical trial are unable to experience future nonfatal outcomes.

To overcome these concerns, Cleland et al. (3) have used a novel approach that relies on a composite outcome, namely “days lost due to death or hospitalization,” over their eight-month follow-up period. (They also separately reported one-year all-cause mortality.) By developing this composite outcome, the investigators have avoided directly equating rehospitalization with death as in a traditional event-free survival analysis, while at the same time allowing for patients to have repeated rehospitalizations. This approach allows clinicians to better appreciate the effect of home telemonitoring on their composite end point and its overall clinical and economic consequences.

Because of recent advances in cardiovascular medicine and lower short-term mortality rates, it has become necessary for many clinical trials to incorporate composite end points into their protocols as a primary outcome in order to demonstrate biological efficacy and statistical significance (1,2). We applaud Cleland et al. (3) for using an innovative and rational composite end point to evaluate a clinically relevant outcome in high-risk patients with heart failure. Their meticulous reporting of each component of their composite end point is also important and should be commended.

Of course, we wonder whether additional methodologies such as “weighting” individual components of a composite end point—days dead are counted more heavily than days hospitalized, for example—may further improve these approaches. Such a strategy of weighting outcomes was used effectively in the recent A-HeFT (African-American Heart Failure Trial) study (4). Perhaps at a minimum, separate reporting of individual components of a composite primary end point should become routine and even integrated into the CONSORT (Consolidated Standards of Reporting Trials) guidelines (1).

REFERENCES


Noninvasive Home Telemonitoring: The Trans-European Network–Home-Care Management System

Cleland et al. (1) for the first time demonstrated that telemedical support in the follow-up of ambulatory patients with chronic heart failure (CHF) compared to usual care is associated with survival benefits as well as reduced length of hospitalization. The greatest financial burden of CHF for society is associated with its high hospitalization rates. Cleland et al. showed that hospitalization rates were reduced in the group of patients receiving telemedical care, but not in patients receiving nurse-led care. Their study sets a new standard in telemedical research. The introduction of future technology will not be possible without investigating the effects on morbidity and mortality.

During the last five years, three generations of telemedical systems have been introduced. The first-generation system was based on sensors typically employing conventional telephone systems to transfer data into central databases, which was then—without analysis—transferred to physicians. The second-generation system involved the use of additional sensors, but the main difference was in the additional processing of the incoming data. The system employed in the study by Cleland et al. (1) represents this approach. The main structural problems of these systems are the divided responsibility in all decision-making processes and that direct patient contact is not utilized. Hence, their medical impact is indirect and delayed.
Nevertheless, this system is faster than a nurse-based system, which might be the reason for its better effectiveness. It would have been interesting to see data on the average time span between problem detection and relay of information to the treating physician and between the time when information was received and execution of changes in patient care. A reduction of this time span—as in acute coronary care—could be the key to further reduce mortality rates, particularly with regards to sudden death. Additional information on the cause of death would have been important. We hypothesize that in the present study, nurse-led care as well as telemedicine, compared to usual care, reduced the occurrence of death due to progressive deterioration of cardiac failure, but not the rate of sudden death. When developing future telemedical systems, we need to carefully evaluate the different parameters for their contribution in making meaningful therapeutic decisions. Do the researchers have data on which information was required in making management decisions?

The medical impact of third-generation telemedical systems will be direct and immediate. Decisions will be based on incoming data, the patient’s history, current treatment, and direct patient contact. Such systems are in development (2). The introduction of these systems will allow development of telemedical systems into tele-home-care networks that assist physicians and nurses in the ambulatory treatment of CHF patients. Havranek (3), suggested that telemedical approaches will be successful when the involved parties know each other. We agree, and we believe that only a third-generation telemedical system will be able to achieve this.

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REPLY

We thank Dr. Chan and colleagues for their compliments about TEN-HMS (Trans-European Network–Home-Care Management System) and its primary end point (1). We agree that time-to-first-event analyses of composite outcomes are difficult to interpret and may be clinically misleading. Time-to-first event analysis is a powerful statistical tool, but it does appear that the “servant has become the master” in the design and analysis of many contemporary clinical trials. Patients with serious, symptomatic conditions have similar goals to most other people; they want to live a long and happy life. The emphasis on well-being and longevity will vary depending on the severity of symptoms and the expectations of the individual. Accordingly, clinical trials should try to capture this information, and composite outcomes are the preferred health measure because neither well-being nor longevity alone describes what most patients want.

Time-to-event analysis is clearly appropriate for mortality but not for most other outcomes in trials of heart failure; this is because it ignores all events subsequent to the first and ignores the potential of many patients to make a good recovery from what may be a minor incident. The reason for the continued popularity of this test is its track record, which has had the unfortunate side effect of suppressing the development of alternatives. There is no doubt that alternatives are required, but these new and more clinically sensible tools also need to be subjected to testing and critical analysis in terms of their internal logic, relevance, and statistical power.

It is clear that the measure of days alive and out of hospital is not going to be a robust end point for most clinical trials because of the skewed distribution and large variation among individuals. Also, hospitalization is generally being used as a surrogate measure for well-being, and the validity of this assumption has not been adequately tested. Outcomes such as “Patient-Journey” or QALY (quality adjusted life-years) are easily measured and describe effects both on well-being and longevity (2). The distribution of derived values is more normally distributed than days alive and out of hospital, and therefore statistical testing is more straightforward and powerful. Very simple quality-of-life or symptom-assessment tools should be used as patients may tire of filling in complex questionnaires repetitively. The method suggested by Dr. Chan and colleagues and variations on that theme used by others is certainly an attractive, alternative method for assessing the effects of therapy (3). However, we believe that this approach is better suited to medium-sized studies investigating the mechanism of drug effect. Such studies provide valuable information that will help decide whether it is worth proceeding to a definitive outcome study and whether its primary end point should be all-cause mortality, “Patient-Journey,” or QALY.

We also thank Drs. Koehler and Anker for their comments. We would have liked to take the credit for being the first study of telemedicine to show a reduction in mortality, but, in fact, we were only the second study to do so (4). Also, the DIAL (ranDomised trial of telephone Intervention in chronic heArt faiLure) study showed a reduction in hospitalizations for heart failure, although not mortality, in a very simple telemedicine project (5). The TEN-HMS trial shows one of the largest absolute differences in mortality for any intervention in heart failure. Accordingly, there is already more evidence of a mortality benefit from telemedicine in heart failure than for many other interventions. It is hoped that the next round of guidelines will recognize the importance of organization of care, which is greatly assisted by telemedicine, for patients with heart failure.

Hospitalization makes up just a small fraction of the patient experience of heart failure. Evolutions and revolutions in care are likely to increase expenditures on out-of-hospital care disproportionately. We believe that the importance of hospital care for patients with heart failure will diminish in the future owing to improvements in treatment, the delivery of care, and the development of hospices for the terminally ill.

Drs. Koehler and Anker rightly point out that telecare is still in its infancy and is only now approaching the threshold of mainstream medicine. Much more work is required on integrating health professionals into this system of care. We are confident that a telemedicine strategy can offer much greater benefit than we...