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EDITORIAL COMMENT

What Is Your Quest?*

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The heart failure community is on a quest to find a surrogate marker that guides us to therapies that improve clinical outcomes and enhance the lives of our patients. We have been on this quest for a long time, and the road is strewn with many failures. In this issue of *JACC: Heart Failure*, Ciani et al. (1) take up the gauntlet by revisiting a previous "candidate"—exercise capacity.

SEE PAGE 596

Before exploring the details of the latest attempt by Ciani et al. (1), it may be helpful to review a few basic concepts, which have been outlined by Fleming and DeMets (2) and, before them, by Prentice (3). For an intermediate outcome to cross the bridge and become a surrogate, it must answer 3 questions. The first obvious question is, does the intermediate outcome correlate with the clinical outcome of interest? There are a few more requirements before a correlate can become a surrogate. The surrogate needs to change with the intervention in the same manner that the intervention will have an impact on the clinical outcome (3). There is also a practical issue: surrogates should show the change closer in time to the treatment and should allow easier detection of an effect (i.e., smaller sample size) than a more distant or less frequent clinical endpoint (3). This speaks to the practical issue, that the primary purpose of a surrogate from a clinical trial perspective is to reduce the time or cost of performing a study.

Clinical research in heart failure has proposed a number of potential surrogates including exercise capacity, structural endpoints of left ventricular dimension, hemodynamic measurements, arrhythmia, autonomic parameters, and biomarkers (4). Unfortunately, none of these has been identified as the "perfect" surrogate marker for mortality and health-related quality of life (HRQOL). For some of these endpoints, including exercise capacity, the "falls from grace" were the clinical trials of inotropes (e.g., milrinone) and vasodilators (e.g., flosequinan), in which exercise capacity improved but survival declined (5,6).

We now arrive at the report by Ciani et al (1). The authors revisited exercise capacity, specifically measured using peak oxygen consumption (Vo_2) and 6-min walk test (6MWT) distance, as the surrogate for mortality, hospitalization, and HRQOL. They found that, in studies evaluating exercise training, changes in both intermediate outcomes did not predict changes in mortality or hospitalization and, thus, were not good surrogate markers for these endpoints. However, both peak Vo_2 and 6MWT distance did prove to be potential surrogates for HRQOL.

It is not surprising that exercise capacity was identified as a potential surrogate marker for HRQOL. Large portions of these instruments relate to fatigue and physical capability of performing tasks. We generally consider an intermediate endpoint an appropriate surrogate if it is also in the causal pathway of the disease and contributes directly to the clinical endpoint of interest. For there not to be a relationship between exercise capacity and HRQOL, there would have to be a large negative impact on other factors that contribute to HRQOL measurements, like edema or mood (e.g., depression). Thus, it would be unlikely that an intervention would improve exercise capacity and not quality of life.

The correlation between exercise capacity and clinical outcomes is the higher bar to clear. Patients with heart failure, particularly as they become Medicare beneficiaries, experience hospitalizations due to a broad array of causes (7). In addition, the number of noncardiac comorbidities, which are highly prevalent

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in older heart failure patients, is correlated with the risk of not only heart failure hospitalizations but all-cause hospitalizations. Underlying these findings are the national trends in the United States showing a decline in the rate of primary heart failure admissions from 2001 to 2014, whereas the non-heart failure admission rate increased from 2001 to 2005 but then returned to the 2001 level by 2014 (8). This would suggest that a therapy targeting a pathophysiological pathway in heart failure that would improve a surrogate marker may not have an impact on hospitalization, particularly if the endpoint is all-cause hospitalization, to the same degree. In similar fashion, given the burden of comorbidities in patients with heart failure, the investigational treatments may have little impact on mortality.

Thus, where does that leave us in our quest for a surrogate marker? We certainly have not "stormed the castle" with exercise capacity. It is likely that exercise capacity correlates with HRQOL in heart failure clinical trials, particularly those trials evaluating exercise-based rehabilitation interventions; but does it really meet the practical criteria required of a surrogate endpoint? Is it easier to identify an effect versus HRQOL that would allow for a smaller sample size? Unlike clinical outcomes that may be rare, every participant, with the exception of those who are censored, is able to contribute to the HRQOL outcome, which reduces the number of participants required to detect a meaningful difference. Although changes in exercise capacity may take place before changes in HRQOL, these changes would have to be dramatic to be sure that HRQOL would be positive. In the current study, changes in peak Vo_2 (5 ml/kg per min) and 6MWT distance (80 m) required to yield a confidence level that an exercise intervention would improve HRQOL by a meaningful amount are not trivial. Peak Vo_2 and 6MWT distance changes represent a 35% and 22% increase, respectively, from baseline in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) participants (9). There are also the practical aspects of feasibility and cost. Cardiopulmonary exercise tests, particularly, are not easy to implement consistently in clinical trials; they can be uncomfortable for subjects, which can lead to drop out and incomplete data; and they carry a cost.

Despite these limitations, exercise capacity will remain an important component of phase 2 studies, and 1 of the signals investigators will turn to as an indicator to move forward with a larger clinical trial. The study by Ciani et al. (1) confirms the ability of peak Vo_2 and 6MWT distance to provide important information regarding how patients will feel with a new treatment. As our ability to consistently measure patient-reported outcomes has improved, we have seen increased focus and value placed on them. Patient-reported outcomes are becoming a pathway for drug and device approval, federal funding is prioritizing studies in the field, and we have a patient-centered outcomes research institute. Having a validated surrogate for quality of life will help in the identification of new treatments for patients with heart failure.

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