The Science of Quality-of-Life-Directed Care!

Javed Butler, MD, MPH; Vasiliki V. Georgiopoulou, MD

Aspirations have no limit, barring reality. The obstacles imposed by reality to temper aspirations can be divided into 3 categories. First are those obstacles that are not negotiable (eg, 24 hours in a day, we all must die). Second are those that are negotiable, easily or with difficulty, but come at an acceptable opportunity cost. Such obstacles often are the foundation of aspirations and inspirations alike; examples of achievements in medicine and elsewhere overcoming them are too numerous to illustrate. Third are those that are negotiable but come only at a high opportunity cost. Here, the devil really does lie in the details, because the definition of opportunity cost is not absolute; hence, the debate. Let us examine the article by Allen et al1 in the current issue of Circulation: Cardiovascular Quality and Outcomes in this framework.

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The primary concern of healthcare providers is to deliver the best treatment to all patients, with an aim to extend longevity and improve quality of life. This concern is even more important for patients with chronic diseases. During the past 2 decades, several drugs and devices have been shown to improve mortality risk from heart failure with depressed ejection fraction.2–4 Allen and colleagues1 very nobly contend that mortality should not be the only outcome that we focus on, and that improving quality of life should be an important aim. How can one disagree with this assertion?

To help to achieve this goal, the authors assessed the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial database5 to identify factors related to 6-month mortality or unfavorable quality of life (defined as Kansas City Cardiomyopathy Questionnaire scores <45) after discharge for decompensated heart failure. As might be expected from a large data set analysis, several variables related to the defined outcome were identified. A risk score was developed that had moderate discrimination (C statistic, 0.72). In a parallel analysis, the authors highlight the fact that the predictors of quality of life were different from those for death or rehospitalization. They conclude that routine clinical characteristics are associated with risk for persistently unfavorable quality of life or death. Interesting, they also conclude that, “such information can target patients for whom aggressive treatment options (eg, devices or transplantation), and end-of-life discussions should be strongly considered before discharge.” The first part of the conclusion is a quantified fact; the second, however, represents a huge leap from quality-of-life-focused to quality-of-life-directed care!

Several issues regarding the analysis need to be highlighted. The EVEREST trial enrolled relatively younger, predominantly white men. Suboptimal quality-of-life burden, manifestation, and predictors might be different in older individuals, in women, and among the various races. Half the heart failure burden is in patients with preserved ejection fraction, and these patients have significant demographic differences than those enrolled in the EVEREST trial.6 Hence, these data are of limited generalizability. Additionally, many characteristics that may determine quality of life (eg, cumulative advanced comorbidity burden) usually are exclusion criteria for enrollment in clinical trials. The C statistic is modest, and there is the possibility of overfitting in the derivation data set without external validation. The goodness-of-fit test indicated borderline fit.

Then there are issues with quality of life as an outcome itself. Are the underlying determinants of quality of life directly relevant to heart failure? This question is rhetorical, but important if one were to contend quality-of-life-directed care. It is interesting to note that there were more smokers among the group with better quality-of-life scores. Mortality is a binary, noncontroversial outcome, and hence, we are better at predicting death. Although the hospitalization event is a binary variable, the decision to admit a patient is not because it represents a subjective decision by the provider in many cases. It is not a surprise, then, that the prediction models for hospitalization risk do not perform as well as those for mortality.7 Quality of life is an even more subjective measure that is truly continuous in nature, which has been artificially dichotomized at a certain score. Instability of the Kansas City Cardiomyopathy Questionnaire score of 45 to define quality-of-life outcomes is of concern because a sizeable proportion of individuals might move in either direction around the defined cut point on a day-to-day basis, regardless of the underlying disease process. It is quite likely that accurate, valid, and reproducible prediction of a quality-of-life assessment that is generalizable may be a difficult task.

In this respect, it is somewhat surprising that Allen et al1 compared predictors of mortality, hospitalization, and quality of life individually as opposed to mortality plus hospitalization versus mortality plus quality-of-life risk prediction. The latter comparison, which is more clinically valid, may not be very different between the 2 options, but we do not know that.

Let us now turn our attention back to the issue of quality-of-life-focused versus -directed care. It is one thing to assess the effect of newer therapies not only for mortality, but also for quality of life. However, Allen et al conclude that

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Table. Impact on Mortality and Quality of Life of Common Heart Failure Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mortality</th>
<th>Hospitalization</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Reduced²</td>
<td>Reduced²</td>
<td>Improved¹¹</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Reduced¹</td>
<td>Reduced¹</td>
<td>Improved¹²</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Reduced¹³</td>
<td>Reduced¹³</td>
<td>Improved¹³</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Neutral¹⁴</td>
<td>Reduced¹⁴</td>
<td>Neutral¹⁵</td>
</tr>
<tr>
<td>Diuretics</td>
<td>?</td>
<td>Improved</td>
<td>symptoms¹⁶</td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>Reduced¹⁷</td>
<td>Reduced¹⁷</td>
<td>Improved¹⁷</td>
</tr>
<tr>
<td>Inotropes</td>
<td>Increased¹⁸</td>
<td>Increased¹⁸</td>
<td>Improved</td>
</tr>
<tr>
<td>Defibrillator</td>
<td>Reduced¹⁹</td>
<td>Increased¹⁹</td>
<td>Worsened²⁰</td>
</tr>
<tr>
<td>Biventricular pacemaker</td>
<td>Reduced²¹</td>
<td>Reduced²¹</td>
<td>Improved²¹</td>
</tr>
<tr>
<td>Left ventricular assist device</td>
<td>Reduced²²</td>
<td>Reduced²²</td>
<td>Improved²²</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Neutral⁰</td>
<td>Neutral⁰</td>
<td>Improved</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

Projected unfavorable quality of life should direct “aggressive treatment options” and “end-of-life discussions.” No data are presented that support this conclusion. Because decisions for advanced therapies or end-of-life care currently are based on mortality risk primarily, we can assume that the novelty of this conclusion is that the risk of poor quality of life should also direct care options. Let us examine this more carefully in terms of heart failure.

The Table describes the effects on mortality, hospitalization rate, and quality of life of common heart failure therapies. In the majority of cases, therapies that reduce mortality also improve quality of life and hospitalization rate. Defibrillators actually may worsen hospitalization rate and quality of life, but the mortality reduction is so remarkable, at least in the populations tested, that it is an accepted therapy nonetheless. Inotropes are remarkable in that they improve symptoms but worsen mortality risk; their routine use, therefore, is not recommended.

If, for most therapies, the benefits are congruent for mortality and quality-of-life effects, the real discussion is related to 3 other possible scenarios. First, should advanced therapies target quality-of-life improvement primarily even if the mortality is not expected to improve, such as transplantation in a patient who is at risk for poor quality of life but who does not meet the criteria for transplantation based on a mortality risk threshold? This is easy! There are just not enough donor organs available to give individuals transplants for improvement in quality of life. Mortality and mortality risk alone should be the primary driver of listing decisions. The second option is to use projected quality of life to plan end-of-life care. This point is moot in most instances because such patients will have a parallel high risk of mortality anyway. Alternatively, the dangers of discussing end-of-life care in a patient not at high risk for mortality but primarily for poor quality of life otherwise does not need a discussion about how slippery a slope that can be.

The third option is to give therapies that improve quality of life and are mortality neutral. One tangential example is dyspnea improvement in acute heart failure. Improving quality of life or symptoms, even if “hard” outcomes do not improve, appears to have a high normative value. However, this circles back to where we initiated our discussion on obstacles and opportunity costs. The Nesiritide in the Vasodilation in the Management of Acute CHF trial⁸ showed improved dyspnea over standard therapy in ≈10% more patients (dyspnea was improved in the majority of the patients with standard of care anyway). The improvement in dyspnea or global clinical status in the nesiritide and nitroglycerin group was not different at 3 hours. During the first 24 hours, no significant differences were found between the nesiritide and nitroglycerin group for dyspnea. For the global clinical status using 1 statistical analytic method, nesiritide compared with nitroglycerin was associated with marginally significant improvement (P=0.04) but was nonsignificant when an alternate analysis was performed. Subsequently, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial) trial⁹ showed no improvement in mortality and hospitalization risk with nesiritide. Nesiritide sales reached $400 million in 2004⁴⁰ before safety concerns regarding mortality and renal function were raised. (Subsequently, these were not validated by the ASCEND trial.) Are these subjective improvements without altering hard outcomes worth it? If cost were not an issue, they are. But what if it costs $400 million annually? We are not sure. The current threat to the US economic outlook related to medical expenditures needs no discussion here. How to invest 400 million medical dollars for the most value may be debated. What we cannot ignore anymore is the cost and opportunity cost in medical decision-making any longer.

This example is tangential because dyspnea is only 1 component of quality of life. But it illustrates the possibility that we have drugs and devices that do not improve the risk for mortality or hospitalization but that only affect subjective quality of life. Improving quality of life is a noble goal that we all should aspire to. Luckily so far, therapies that improve quality of life generally tend to improve hard outcomes as well. However, in instances where they do not, one has to carefully balance the degree of improvement in quality of life for a given cost for 1 disease versus investment in research or treatment of another. As for quality-of-life scores actually directing care, there are many details that need to be sorted out. Allen and colleagues have done a fantastic analysis that highlights a bold new concept. They should be congratulated for moving us on a path for further research and discovery toward this humane goal.

Disclosures

None.

References


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