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Changing Preferences for Survival After Hospitalization With Advanced Heart Failure

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Objectives This study was designed to analyze how patient preferences for survival versus quality-of-life change after hospitalization with advanced heart failure (HF).

Background Although patient-centered care is a priority, little is known about preferences to trade length of life for quality among hospitalized patients with advanced HF, and it is not known how those preferences change after hospitalization.

Methods The time trade-off utility, symptom scores, and 6-min walk distance were measured in 287 patients in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) trial at hospitalization and again during 6 months after therapy to relieve congestion.

Results Willingness to trade was bimodal. At baseline, the median trade for better quality was 3 months' survival time, with a modest relation to symptom severity. Preference for survival time was stable for most patients, but increase after discharge occurred in 98 of 145 (68%) patients initially willing to trade survival time, and was more common with symptom improvement and after therapy guided by pulmonary artery catheters ($p = 0.034$). Adjusting days alive after hospital discharge for patients' survival preference reduced overall days by 24%, with the largest reduction among patients dying early after discharge ($p = 0.0015$).

Conclusions Preferences remain in favor of survival for many patients despite advanced HF symptoms, but increase further after hospitalization. The bimodal distribution and the stability of patient preference limit utility as a trial end point, but support its relevance in design of care for an individual patient. (J Am Coll Cardiol 2008;52:1702–8)

Advances in the treatment of heart failure (HF) have delayed disease progression and prolonged survival. Earlier use of neurohormonal antagonists and devices has diminished untimely sudden death, leaving more patients with symptoms of advanced HF (1). As the symptomatic burden is borne for a longer period of time, it becomes increasingly important to understand the utility awarded by patients to survival, and how this may change. The Institute of Medicine advocates progress toward patient-centered care (2), in which individual preferences are crucial and the patient is empowered in therapeutic decision making. Yet, there is little understanding about the trajectory of patient preferences in HF.

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Many scales and questionnaires probe symptoms in HF, but these scores do not equate to the importance of survival to an individual patient. The time trade-off (TTO) tool offers direct assessment of relative value placed by patients on survival time versus perceived symptomatic health (3). A study of the TTO utility done by Jaagosild et al. (4) showed a high preference for survival among a heterogenous population of patients surviving

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HF in an intensive care unit setting without specified intervention. A previous study by Lewis et al. (5) showed a lower preference for survival in severe HF, and Havranek et al. (6) have shown this measure to correlate with activity. It is not known how the preferences of hospitalized patients may change after discharge.

This study was planned within the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) study to understand how utilities defined by hospitalized patients with advanced HF change after therapy designed to relieve congestive symptoms. The hypothesis was that changes in patient preference would be frequent and linked to improvements in symptoms and functional capacity after hospitalization. In addition, the study pre-specified exploration of a novel secondary end point of survival days adjusted by repeated TTO utilities.

Methods

The ESCAPE study was sponsored by the National Heart, Lung, and Blood Institute to compare therapy guided by clinical assessment alone with therapy guided by clinical assessment and pulmonary artery catheter (PAC) monitoring on the primary end point of days alive out of the hospital for 6 months. Criteria included current hospitalization with at least 1 symptom and 1 sign of congestion, previous HF hospitalization or usual daily dose of ≥160 mg furosemide, left ventricular ejection fraction <30%, and systolic blood pressure <125 mm Hg. Patients were excluded for creatinine >3.5 mg/dl, milrinone use, or >3 μg/kg/min dopamine or dobutamine.

Informed consent was obtained before baseline assessment. After randomization, therapy was adjusted in both arms with the goals of an estimated jugular venous pressure of ≤8 cm and resolution of orthopnea and edema, assessed qualitatively using a 0 to 4 scale. Additional hemodynamic goals for patients receiving PAC were pulmonary capillary wedge pressure ≤15 mm Hg and right atrial pressure ≤8 mm Hg.

The TTO instrument was administered verbally by the study nurse at 1, 2, 3, and 6 months. Whenever possible, this instrument and written questions were administered in the absence of family. After a scripted introduction, the initial question was "Would you prefer living 2 years in your current state of health or living 1 day in excellent health?" An answer of 1 day, equated to a utility of 1/730 (~0), would end the script. An answer of 2 years would be followed by the next choice, between living "2 years in your current state of health or living 1 year 11 months in excellent health." After sequential choices, the number of months (≤24 months) in excellent health that the respondent considered to be equivalent in value to 24 months of survival in current health was recorded, and this ratio was the utility (between 0 and 1). The number of months at the indifference point subtracted from 24 yielded the number of months of survival time that the patient would be willing to trade.

The TTO instrument, the Minnesota Living with Heart Failure (MLHF) questionnaire, and visual analog scales of global health, dyspnea, and individual worst symptom were completed at baseline, and patients performed the 6-min walk test if possible. At 1, 2, 3, and 6 months, patients repeated the time trade-off. At 3 months, patients repeated all measurements assessed at baseline.

Abbreviations and Acronyms

CAD = coronary artery disease
HF = heart failure
MLHF = Minnesota Living with Heart Failure
PAC = pulmonary artery catheter
TTO = time trade-off

The design of the ESCAPE trial pre-specified a new secondary end point, the "preferred survival days," the sum of the days alive during 6 months after hospital discharge, adjusted by serial TTO scores (maximum 180 days). This was calculated by weighting days alive in each interval (baseline to 1, 1 to 2, 2 to 3, and 3 to 6 months) by the mean of the TTO values bracketing that interval, and summing across intervals (days between discharge and 1 month were weighted only by the 1-month value). Thus, a day alive in an interval during which the patient preferred to trade 12 of 24 months for better health would count as 0.5 day, compared with 1 day if the patient was unwilling to trade any survival time. Days hospitalized or dead were designated with a value of 0.

Statistical methods. Baseline characteristics are summarized for TTO groups as percent for categorical variables and median for continuous variables. Continuous variables were compared across TTO groups using the Kruskal-Wallis tests. Categorical variables were compared across TTO groups using ordinal logistic regression with the TTO group as the response and the variable of interest as the predictor. (Patients with missing baseline data are described in Table 1 and not included in other current analyses; patients without data at either 3 or 6 months are not included in the analysis of changing preferences.) The skewed distribution of responses (Fig. 1) suggested grouping into 4 levels for baseline characteristics and for frequency of change between groups. (Division by quartiles would have arbitrarily separated patients with the same discrete values.) This was a survivors' analysis without imputation for death or absence of serial studies. When both the 3- and 6-month results were available, the one with largest absolute change from baseline was used.

Magnitude of change in functional scores was compared among groups defined by TTO change using Wilcoxon rank sum tests. Direction of maximum change in TTO preference (willing to change more, no change, willing to trade less) was compared between randomized treatments using a Mantel-Haenszel chi-square test. The same test was used to determine the relationship between actual survival and the adjustments by patient preference for survival.

Results

TTO distribution. The TTO values were available for 404 patients at the time of randomization during hospitaliza-

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Table 1 Characterization of Patients With Missing TTO Data at Baseline or Follow-Up

Baseline Factor	Patients Without Baseline TTO Data (n = 29)	Patients With Baseline TTO Who Survived Without Follow-Up TTO Data (n = 62)	Patients With Baseline and TTO Data at 3 and/or 6 Months (n = 287)
Male gender, %	79	68	75
Ethnic/racial minority, %	45	47	39
LVEF, %	20 (15, 25)	19 (15, 20)	20 (15, 25)
SBP, mm Hg	98 (90, 110)	101 (93, 113)	106 (95, 118)
BUN, mg/dl	37 (26, 54)	26 (17, 41)	27 (19, 38)
BNP, pg/ml	976 (477, 1,952)	585 (257, 1,042)	511 (193, 1,044)
6-min walk, m	37 (0, 162)	8 (0, 162)	135 (6, 260)
JVP, cm (%)			
<8	10	12	8
8–12	28	40	41
12–16	41	17	31
>16	21	12	20
Edema, %			
0–1+	65	64	68
3–4+	17	11	11
Freedom from worst symptom (0–100; 100 = best)	40 (20, 55)	30 (20, 50)	35 (20, 50)
Global score	35 (28, 52)	40 (30, 50)	40 (30, 60)
MLHF score	75 (66, 82)	73 (58, 84)	76 (65, 87)

Data are presented as median (25th, 75th percentiles) unless otherwise indicated.

BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; JVP = jugular venous pressure; LVEF = left ventricular ejection fraction; MLHF = Minnesota Living with Heart Failure questionnaire; SBP = systolic blood pressure; TTO = time trade-off.

tion. The distribution was bimodal, with most values at the extremes (Fig. 1). Many patients (49%) expressed almost no willingness to trade time at baseline (≤1 month of total possible 24 months). The next most common response (28%) was to trade almost all time to feel better for the remaining time (scores closest to 0). The remainder of the responses were scattered, with small peaks at 6, 12, and 18 months. Based on these results, patients were grouped into 4 levels: willing to trade almost all time (22 to 24 months) and willing to trade little or no time (0 time or up to 2 of 24 possible months); then the remainder were divided at the 12-month value (12 to 21 months traded vs. 3 to 11 months traded) (Table 2). The baseline demographics and resting clinical parameters did not distinguish between these 4 preference groups at the time of hospitalization, as trial design mandated presence of symptoms and signs of ele-

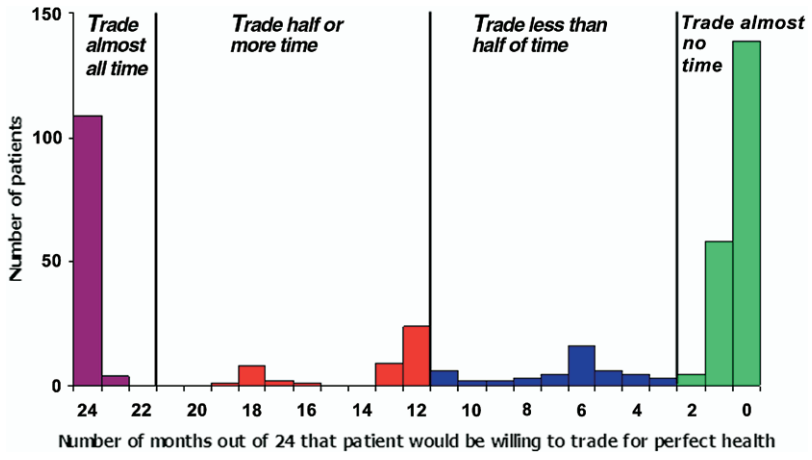

Figure 1 Bimodal Distribution of Patient Preferences

Histogram showing distribution of time trade-off values at baseline. The x-axis is expressed in terms of months traded, such that 24 months indicates that the patient awards no value to survival at the current state of health, and 0 months traded indicates full value. These month-values can be changed into a utility from 0 to 1 by subtracting from 24 months and then expressing as a fraction of 24. The values have been divided symmetrically into 4 ranges for group description and analysis of major changes.

Table 2 Characteristics of Patients Grouped by Baseline TTO Levels

Characteristic	Willing to Trade Almost All Time, 22–24 Months (n = 112)	Willing to Trade One-Half or More Time, 12–21 Months (n = 45)	Willing to Trade Less Than One-Half of Time, 3–11 Months (n = 46)	Willing to Trade Almost No Time, 0–2 Months (n = 201)
Age, yrs	54 (45, 65)	58 (49, 63)	59 (49, 72)	56 (46, 66)
Male gender, %	71	78	80	73
Minority, %	41	42	30	41
CAD, %	53	64	42	53
LVEF, %	20 (15, 25)	15 (15, 25)	20 (15, 25)	20 (15, 24)
SBP, mm Hg	103 (96, 118)	102 (94, 115)	100 (94, 118)	106 (93, 116)
BUN, mg/dl	27 (19, 40)	29 (20, 46)	32 (24, 51)	27 (17, 41)
BNP, pg/ml	574 (276, 1,199)	575 (344, 1,395)	681 (223, 1,107)	528 (159, 1,089)
6-min walk, m*	60 (0, 169)	169 (0, 198)	198 (46, 299)	113 (0, 256)

Data are presented as median (25th, 75th percentiles) unless otherwise indicated. *Difference in 6-min walk across groups ($p < 0.003$).
CAD = coronary artery disease; other abbreviations as in Table 1.

vated filling pressures. For patients able to perform the 6-min walk test, average distance was shorter than a city block for patients willing to trade at least one-half of their time (Table 2).

Baseline patient preference data was absent in 29 patients, who had symptoms similar to patients providing responses (Table 1). Repeat assessment of preferences at 3 or 6 months was available for 287 patients, at 3 months for 270, and at 6 months for 210 patients. Of the 117 patients without follow-up preference data, 55 had died during the 6 months; the other 62 patients are characterized in Table 1. There is no information on how often attempts were repeated to obtain these missing data. Patients missing follow-up data were similar to patients with follow-up data, but blood pressure and 6-min walk distance were lower.

Of the 287 patients with values at baseline and at 3 to 6 months, 193 had data at both 3 and 6 months, which yielded the same result for 142 patients. When the values differed between 3 and 6 months, 24 patients were better at 3 months and 27 were better at 6 months; the greatest absolute change from baseline classified the overall change after hospitalization. Baseline and 3-month data were available without 6-month data for 77 patients, and baseline and 6-month data were available without 3-month data for 17 patients.

The severity of symptoms was related to the amount of time to be traded at baseline but the relationship became more obvious at 3 months, when clinical status may have been more stable. The correlation between individual components and the TTO was strongest for the MLHF score at 3 months, but even this correlation coefficient was only 0.33, indicating wide individual variation. The specific item regarding depression in the MLHF instrument was associated with the TTO value at baseline and 3 months (both $p < 0.001$).

Changes in TTO and functional status after hospitalization. The average TTO score changed by only 4% (1/24 months) on repeat assessment, with little change after the first post-discharge assessment (Fig. 2). Quantum change over time was measured as movement from one to another of the 4 levels defined in Table 2. Of 287 patients in whom serial measurements were made, the largest group was the 109 patients who initially had the maximum survival preference at baseline—thus, no range for increase—and did not decrease to a lower level (Fig. 3). The most common change overall was an increased level of preference for survival, which occurred in 98 of 145 (68%) patients who began below the maximum level of survival preference. During serial assessment, 25 patients remained willing to trade almost all time, and 9 had mid-level preference levels that did not change (Fig. 3). Only 46 of 212 (23%) patients in the range from which survival preference could worsen expressed a diminishing preference for survival.

Symptoms, 6-min walk distance, and MLHF scores remained improved compared with baseline for the majority of surviving patients. The MLHF scores remained improved in 80% of patients at 6 months. For patients whose preferences did change, those with improved preferences for survival were more likely to have substantial improvement in their worst symptom and in the MLHF questionnaire (Table 3). Changes in preference at 3 months after hospitalization were associated with changes in the depression component of the MLHF questionnaire ($p = 0.0017$). Patients with improved preference were more likely to have experienced an improvement in at least 2 functional measurements (83% vs. 59%, $p < 0.01$).

TTO and trial end points. Change in the TTO assessment throughout the 6 months after discharge was a pre-specified secondary end point in the ESCAPE trial. At each time point (1, 2, 3, and 6 months), there was greater increase in months of preferred survival in the PAC arm than in the clinical arm, as previously reported (7). Using the current analysis for the 4 preference levels defined post-hoc, there were similar levels of improvement (41% vs. 37%) and worsening (15% vs. 22%) in the 2 groups at 3 months. When the greatest level of improvement during the 6 months was analyzed, there was significantly more improvement (46% vs. 36%) and less worsening (22% vs. 32%) in the PAC arm ($p = 0.034$). Slightly lower baseline values of survival preference in the PAC arm may have allowed more evidence of improvement. Approximately one-third of patients in each strategy group had no change in preference over time.

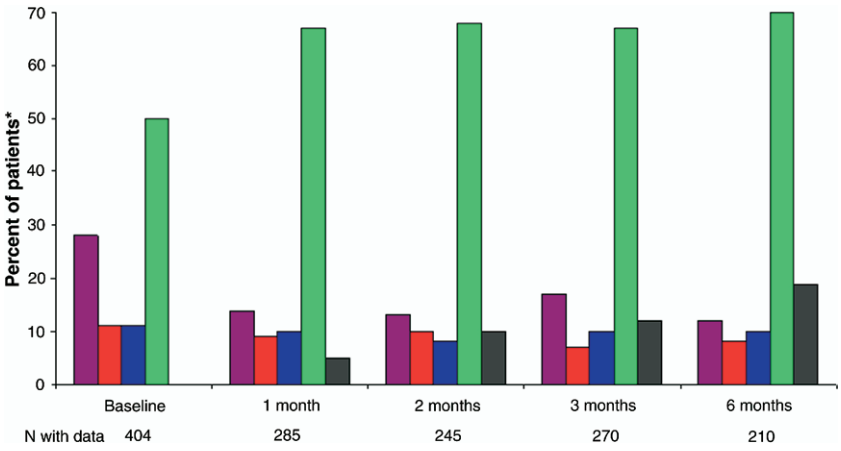

Figure 2 **Changing Patient Preferences After Hospital Discharge**

The proportions of patients in each time trade-off group at different times after hospital discharge are shown. The number of patients responding for each interval is shown below the figure. **Purple bars** = willing to trade almost all (22 to 24 months); **red bars** = willing to trade one-half or more (12 to 21 months); **blue bars** = willing to trade less than one-half (3 to 11 months); **green bars** = willing to trade almost none (0 to 2 months); **black bars** = cumulative number of patients dying by the end of each interval. Definitions of intervals are as in Table 2. *Patients in each willingness-to-trade category at each interval are shown as percent of patients with data at that interval; cumulative deaths are shown as percent of 404 patients with baseline data.

The ESCAPE trial design pre-specified a novel secondary end point defined by adjusting the days alive out of the hospital by the TTO value awarded by the patient to survival during each of the intervals after discharge. As shown in Figure 4, this adjustment reduced the number of valued days from the number of all days by an average of 24% with a wide standard deviation (32%), median reduction 5%. However, the devaluation of survival time was highest in the group with the shortest survival, indicating that those *most* likely to die were *least* likely to have cared about prolonging survival. Of 29 patients surviving <105 days, 9 (31%) indicated that they would trade >90% of their survival days to feel well for the time remaining, compared with 6% of patients surviving all 180 days ($p = 0.0015$).

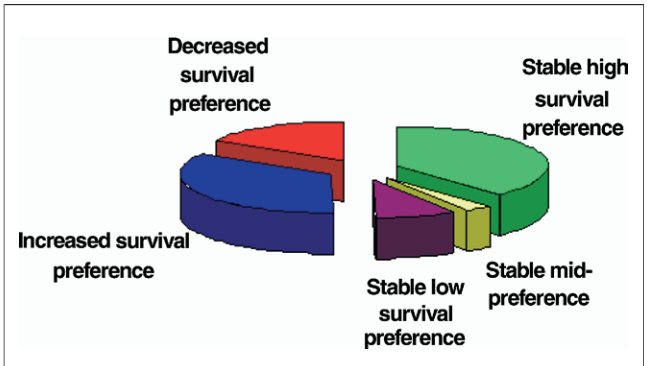

Figure 3 **Stability of Survival Preference**

The pie graph shows the proportions of 287 patients with stable or changing preferences in the 6 months after hospital discharge. Change was defined as movement between the 4 preference levels described in Table 2. Patients remaining in the highest survival preference are "stable high"; those remaining in the lowest survival preference are "stable low." Patients remaining in 1 of the 2 other time-trade off groups are "stable mid-preference." Although the majority of patients demonstrated no change in preference, more patients described an increase than a decrease in preference for survival.

Discussion

This study provides new insight into how often patient preferences change toward survival versus quality of life. Willingness to trade remained largely bimodal, with more patients unwilling to trade any time than willing to trade almost all remaining time in order to enjoy better health. Most patient preferences were stable after hospitalization, but increases from one level to another were twice as common as decreases. Most patients had sustained symptomatic improvement, which was somewhat greater in patients with an increased survival preference. Therapy guided by the PAC in the hospital was associated with a slightly greater increase in preference for survival. Adjustment of days alive for patient preference decreased total days by a small amount, which was most substantial when survival time was short.

Changing patient preferences and symptoms. The TTO instrument, studied in other chronic diseases (6,8,9), integrates multiple factors that determine patient priorities (5,10). In previous studies, the TTO has been assessed during intensive care (4) or stable outpatient care (5). Prospective serial assessment in the ESCAPE trial helps map the trajectory of patient preferences from decompensation in hospital through the transition to the chronic outpatient setting. Patient preferences were relatively stable over time, particularly when survival preference was high at baseline (Fig. 3). The largest group of patients (38%) was

Table 3 Improvement in Functional Parameters by 3 Months in Relation to Changing Preferences

Functional Parameter of Improvement*	Increased Survival Preference at 3 Months (n = 86)	Decreased Survival Preference at 3 Months (n = 50)	Total Number With Changing Preferences and Repeated Parameter Measurement (n = 136)	p Value
Patient global health VAS	+19 (28)	+8 (27)	95	0.126
Breathing VAS	+12 (31)	+9 (22)	49	0.56
Freedom from worst symptom VAS	+25 (31)	+8 (23)	92	0.0065
MLHF score	−22 (23)	−10 (25)	94	0.014
6-min walk, m	130 (123)	100 (166)	59	0.27
Improvement in at least 2 of the above†	83%	59%	96	0.011

Data are presented as mean (SD), except for the last row. All p values from Wilcoxon rank sum tests except the last value, which is from likelihood ratio chi-square test. *Indicated by "+" for all measurements except MLHF (Minnesota Living with Heart Failure) questionnaire, in which lower scores reflect less limitation. †Defined as increase of at least 10 for visual analog score (VAS), decrease of at least 5 for MLHF, and increase of at least 15 m (50 ft) for 6-min walk distance.

unwilling to trade substantial time at baseline and remained unwilling to trade, always preferring to live as long as possible. Change was more likely among patients who placed less value on survival during their decompensation, in whom preference for survival was twice as likely to increase as decrease after hospital discharge. Improvements in preferences seen by 1 month were generally sustained during the remainder of the trial. This improvement may reflect recovery after a transient dip in survival preference at hospitalization, or improvement to a survival preference above that before hospitalization.

The TTO correlated directionally, although modestly and nonlinearly, with symptoms and function, and also correlated with depression. As for angina (10), many patients with severe symptoms remained unwilling to trade time, whereas others with moderate symptoms would trade considerable time. Individual factors such as family dynamics, religious beliefs, and financial burden may play a strong role in preferences. Thus, HF symptoms are only 1 dimension of patient preference for survival, but together with patient education and coping skills, they are probably the most amenable to medical intervention. Symptoms improved in most patients, with greater improvement in patients who had increased preferences for survival after discharge. Symptoms and functional capacity may contribute more to the *changes* in preferences than to the *absolute* preferences, for which the nonmedical determinants may not often change during brief follow-up. Preference for survival over perceived quality of life cannot be inferred from the quality scores alone.

Impact of therapy during hospitalization. The TTO questionnaire indicated slightly but significantly more improvement in preference for survival among patients whose hospital therapy had been guided by the PAC. Dyspnea and

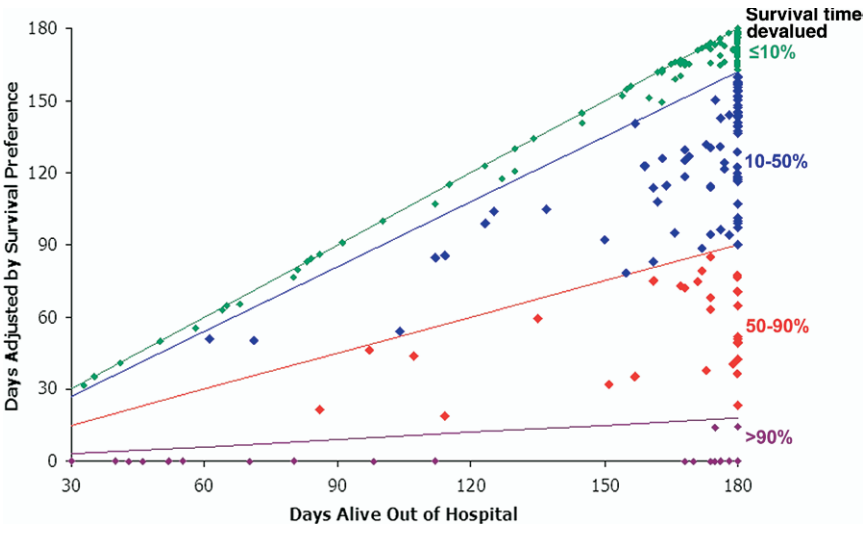

Figure 4 Patient-Preferred Survival

Days alive adjusted by time trade-off. For each patient, the x-y plot compares the actual survival days during 6 months to the survival days adjusted for the survival preference described by the patient during each interval (see Methods). Overall, the majority of patients had <10% devalued days. Patients dying before 105 days had the highest proportion of days devalued by low preference for survival (p = 0.0015), with 31% of patients indicating that they would trade >90% of their remaining days to feel better, compared with 6% of patients surviving all 180 days.

jugular venous distention correlate with willingness to trade time to feel better (5). Patients in both arms of the ESCAPE trial had similar degrees of relief in the hospital, although there was slightly more diuresis, better renal function, and more reduction of mitral regurgitation during reduction of filling pressures measured by the PAC (11). The improvement in the MLHF score was significantly greater at 1 month for patients after PAC-guided therapy (7). The invasive nature of PAC may have conferred a stronger sense of therapeutic efficacy, creating an expectation of greater improvement. It is also possible that the apparent impact of PAC on patient preference was a chance finding.

Preference-adjusted survival. Survival adjusted for patient preference was pre-specified during the design of the ESCAPE trial. Previous trials reporting quality-adjusted life-years for HF populations have generally imputed utilities based on symptom scores (12,13). Adjusting the actual days alive out of hospital by the utility function of how the patients valued their days integrates survival and quality from the patients' standpoint, without introducing assumptions based on our own attitudes. Adjustment for patient value diminished the counted number of days by <10% for most patients (Fig. 4). However, the diminution was most profound for patients who survived <3 months, 31% of whom stated willingness to trade >90% of their remaining days to feel better. It is a vital paradox that the patients *most* likely to contribute mortality end points may be those to whom the length of survival seems *least* important.

Study limitations. This trial is limited by missing data for TTO preferences and symptoms, which have plagued other trials of advanced HF in which such measures are not primary end points (14). Analysis of patients for whom preference data are missing revealed few differences in baseline characteristics, with the exception of patients missing because of death, for which quality is undeterminable. Death was excluded rather than assigned a worst rank, because the study addressed quality of life for survivors, who face therapeutic choices. This and other trials highlight the imperative to increase attention to quality-of-life data completion during monitoring.

The TTO and other utility tools are limited by the hypothetical nature of the questions. Facing imminent mortality, patients may prefer survival over comfort. However, the TTO has been used extensively in oncology (8,9), and it correlates well with the standard gamble (5,15). Although it is clear that preferences should be reviewed often, the optimal mode of assessment has not been established.

Conclusions

Centering care with the patient. This study highlights the complexity of patient-centered care for chronic HF. Because preferences often differ between patients with similar symptoms, our assumptions based on symptom burden may not adequately guide therapy. Most patients prefer survival even during decompensation, and patients who would trade survival time are those most likely to change their preference. These findings suggest a framework of care in which survival preferences would be best assessed after hospital discharge. Further study is necessary to understand how elucidation of patient preferences should guide decisions regarding medical and device therapy, resuscitation, and new therapies for advanced disease.

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Key Words: heart failure ■ quality of life ■ health utilities ■ hospitalization ■ cardiomyopathy.