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Changing Preferences for Survival After Hospitalization with Advanced Heart Failure

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Abstract

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-minute walk were measured at hospitalization and again in 287 patients during 6 months after therapy to relieve congestion in the ESCAPE trial.

Results—Willingness to trade was bimodal. At baseline, the median trade for better quality was 3 months survival time, with modest relation to symptom severity. Preference for survival time was stable for most patients, but increase after discharge occurred in 98/145(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 out of hospital for patients' survival preference reduced overall days by 24%, with largest reduction in patients dying early after discharge (p=0.0015).

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Conclusions—Preferences remain in favor of survival for many patients despite advanced HF symptoms, but increase further after hospitalization. The bi-modal distribution and stability of patient preference limit utility as a trial endpoint, but support its relevance in design of care for an individual patient.

Keywords

heart failure; quality of life; health utilities; hospitalization; cardiomyopathy

Introduction

Advances in the therapy of heart failure (HF) have delayed disease progression and prolonged survival. Earlier use of neurohormonal antagonists and devices have diminished untimely sudden death, leaving more patients with symptoms of advanced HF [1]. As the symptomatic burden is borne longer, 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], where 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 heart failure.

Many scales and questionnaires probe symptoms in HF, but these scores do not equate to the importance of survival to an individual. The time trade-off tool offers direct assessment of relative value placed by patients on survival time versus perceived symptomatic health. [3] A study of the time trade-off utility done by Jaagosild showed high preference for survival[4] in a heterogenous population of patients surviving HF in an ICU setting without specified intervention. Previous study by Lewis showed lower preference for survival in severe HF, [5] and Havranek has shown this measure to correlate with activity. [6] It is not known how preferences of hospitalized patients may change after discharge.

This study was planned within the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) 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 endpoint of survival days adjusted by repeated time trade-off utilities.

METHODS

ESCAPE was sponsored by the National Heart, Lung, and Blood Institute to compare therapy guided by clinical assessment alone to therapy guided by clinical assessment and pulmonary artery catheter (PAC) monitoring on the primary endpoint of days alive out of 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 ≥ 160 mg furosemide, LVEF <30%, and SBP <125 mm Hg. Patients were excluded for creatinine >3.5 mg/dL, milrinone use or over 3 mcg/kg/min of dopamine or dobutamine.

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

The time trade-off 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 (approximately zero), 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 ($\leq$ 24 months) in excellent health that the respondent considered to be equivalent in value to 24 months 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 time trade-off instrument, 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 six minute walk test as possible. At 1, 2, 3, and 6 months, patients repeated the time trade-off. At 3 months, patients repeated all measurements assessed at baseline.

The design of ESCAPE pre-specified a new secondary endpoint, the "preferred survival days," the sum of the days alive out of hospital during 6 months after discharge, adjusted by serial time trade-off scores (maximum 180 days). This was calculated by weighting days alive in each interval (baseline to 1 month, 1 to 2 months, 2 to 3 months, and 3 to 6 months) by the mean of the time trade-off 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 to 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 time trade-off groups as percent for categorical variables and median for continuous variables. Continuous variables were compared across TTO groups using Kruskal-Wallis tests. Categorical variables were compared across TTO groups using ordinal logistic regression with TTO group as the response and the variable of interest as the predictor. Patients with missing baseline data are described in table 2 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 (Figure 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 time trade-off change using Wilcoxon rank sum tests. Direction of maximum change in time trade-off 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. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Time Trade-Off Distribution

Time trade-off values were available for 404 patients at the time of randomization during hospitalization. The distribution was bimodal with most values at the extremes (Figure 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 in order 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 as willing to trade almost all time (22–24 months), willing to trade little or no time (0 time or up to 2 months/24), then the remainder were divided at the 12 month value (12–21 months traded versus 3–11 months traded) (Table 1). 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 elevated filling pressures. For patients able to perform the 6-minute walk, average distance was shorter than a city block in patients willing to trade at least half of their time (Table 1).

Baseline patient preference data was absent in 29 patients, who had symptoms similar to patients providing responses (Table 2). Repeat assessment of preferences at 3 or 6 months was available for 287 patients, at 3 months in 270 and at 6 months in 210 patients. Of the 117 without follow-up preference data, 55 had died during the 6 months, the other 62 patients are characterized in Table 2. There is no information on how often attempts were repeated to obtain this missing data. Patients missing follow-up data were similar to those with follow-up data, but blood pressure and 6-minute walk distance were lower.

Of the 287 patients with values at baseline and at 3–6 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 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 in 77 patients, and baseline and 6 month data were available without 3 month data in 17 patients.

The severity of symptoms was related to the amount of time to be traded at baseline but became more obvious at 3 months, when clinical status may have been more stable. The correlation between individual components and the time trade-off 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 time trade-off value at baseline and three months (both $p<0.001$).

Changes in Time Trade-Off and Functional Status After Hospitalization

The average time trade-off score changed by only 4% (1 of 24 months) on repeat assessment, with little change after the first post-discharge assessment (Figure 2). Quantum change over time was measured as movement from 1 to another of the 4 levels defined in Table 1. 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. (Figure 3). The most common change overall was an increased level of preference for survival, which occurred in 98/145 (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 which did not change (Figure 3). Only 46 of 212 (23%) patients in the range from which survival preference could worsen expressed a diminishing preference for survival.

Symptoms, 6 minute walk, and MLHF scores remained improved compared to baseline in 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 (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 two functional measurements (83 % vs 59%, $p < 0.01$).

Time Trade-Off And Trial Endpoints

Changes in the time trade-off assessment throughout the 6 months after discharge was a pre-specified secondary endpoint 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 CLIN 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.

The ESCAPE design pre-specified a novel secondary endpoint defined by adjusting the days alive out of hospital by the time trade-off 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 24% with a wide SD (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 less than 105 days, 9 (31%) indicated that they would trade more than 90% of their survival days to feel well for the time remaining, compared with 6% of those patients surviving all 180 days (p=0.0015).

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 increased survival preference. Therapy guided by the PAC in hospital was associated with slightly more 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 time trade-off instrument, studied in other chronic diseases [6, 13, 14], integrates multiple factors that determine patient priorities[5, 8]. In previous studies, the time trade-off 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 (Figure 3). The largest group of patients (38%) were unwilling to trade substantial time at baseline and remained unwilling to trade, always preferring to live as long as possible. Change was more

likely in 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 one month were generally sustained during the remainder of the trial. This may reflect recovery after a transient dip in survival preference at hospitalization, or improvement to a survival preference above that prior to hospitalization.

The time trade-off correlated directionally although modestly and non-linearly with symptoms and function, and also correlated with depression. As for angina [8], many patients with severe symptoms remained unwilling to trade time, while 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. HF symptoms are thus only one dimension of patient preference for survival, but, together with patient education and coping skills, are probably the most amenable to medical intervention. Symptoms improved in most patients, with greater improvement in patients who 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 non-medical 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 time trade-off questionnaire indicated slightly but significantly more improvement in preference for survival among patients whose hospital therapy had been guided by the PAC. Dyspnea and 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 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. [9] The improvement in the MLHF score was significantly greater at 1 month in 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 design of the ESCAPE trial. Previous trials reporting quality adjusted life years for HF populations have generally imputed utilities based on symptom scores. [10, 11] 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 (Figure 4) by less than 10% for most patients. However, the diminution was most profound for patients who survived less than 3 months, 31% of whom stated willingness to trade over 90% of their remaining days to feel better. It is a vital paradox that the patients *most* likely to contribute mortality endpoints may be those to whom the length of survival seems *least* important.

Limitations

This trial is limited by missing data for time trade-off preferences and symptoms, which has plagued other trials of advanced HF in which such measures are not primary endpoints. [12] Analysis of patients for which preference data is missing revealed few differences in baseline characteristics, with the exception of patients missing due to 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 time trade-off and other utility tools are limited by the hypothetical nature of the questions. Facing imminent mortality, patients may prefer survival over comfort. However, the time trade-off has been used extensively in oncology [13, 14], and has correlated 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.

Centering Care with the Patient

This study highlights the complexity of patient-centered care for chronic heart failure. 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 those 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.

Acknowledgments

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Abbreviations

BNP, b-type natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness; HF, heart failure; LVEF, left ventricular ejection fraction; MLHF, Minnesota Living with Heart Failure questionnaire; PAC, pulmonary artery catheter; SBP, systolic blood pressure; TTO, time trade-off result (range 0 – 1, 1 = unwilling to trade any survival time).

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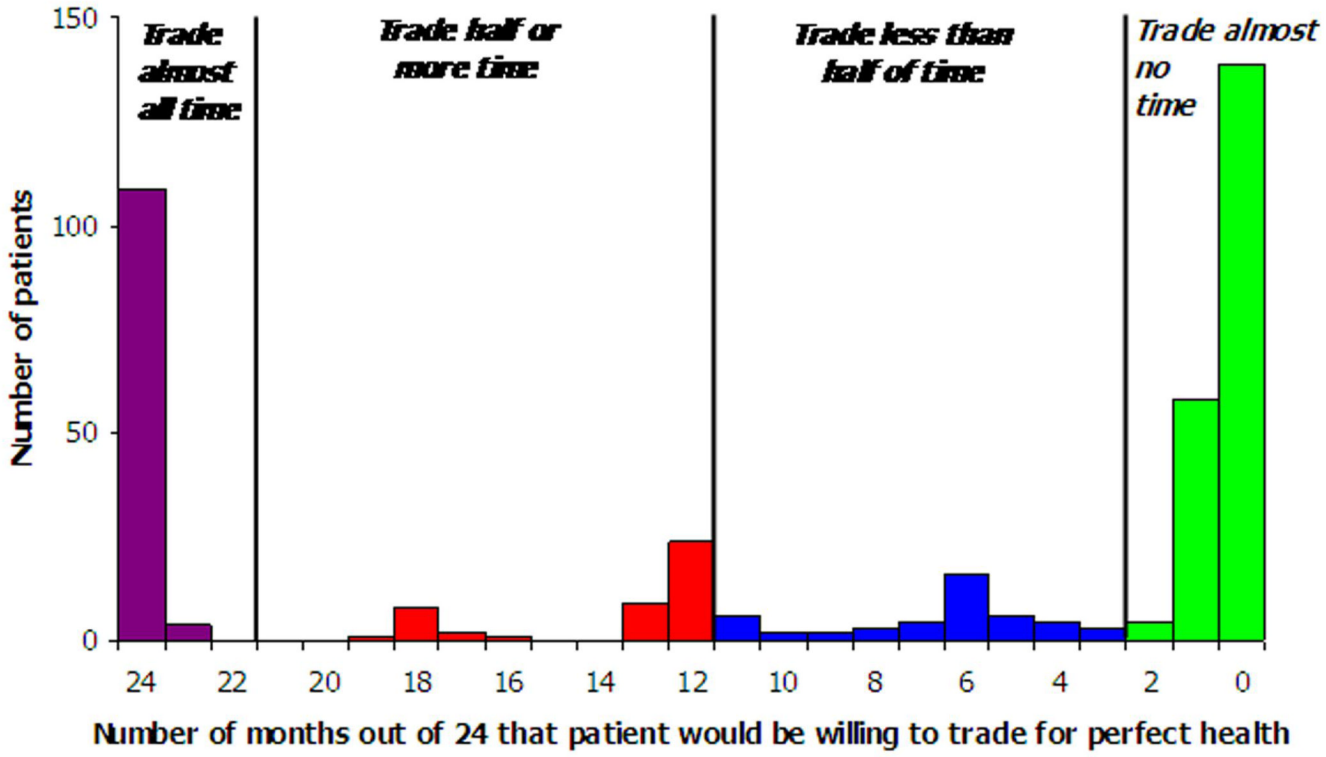
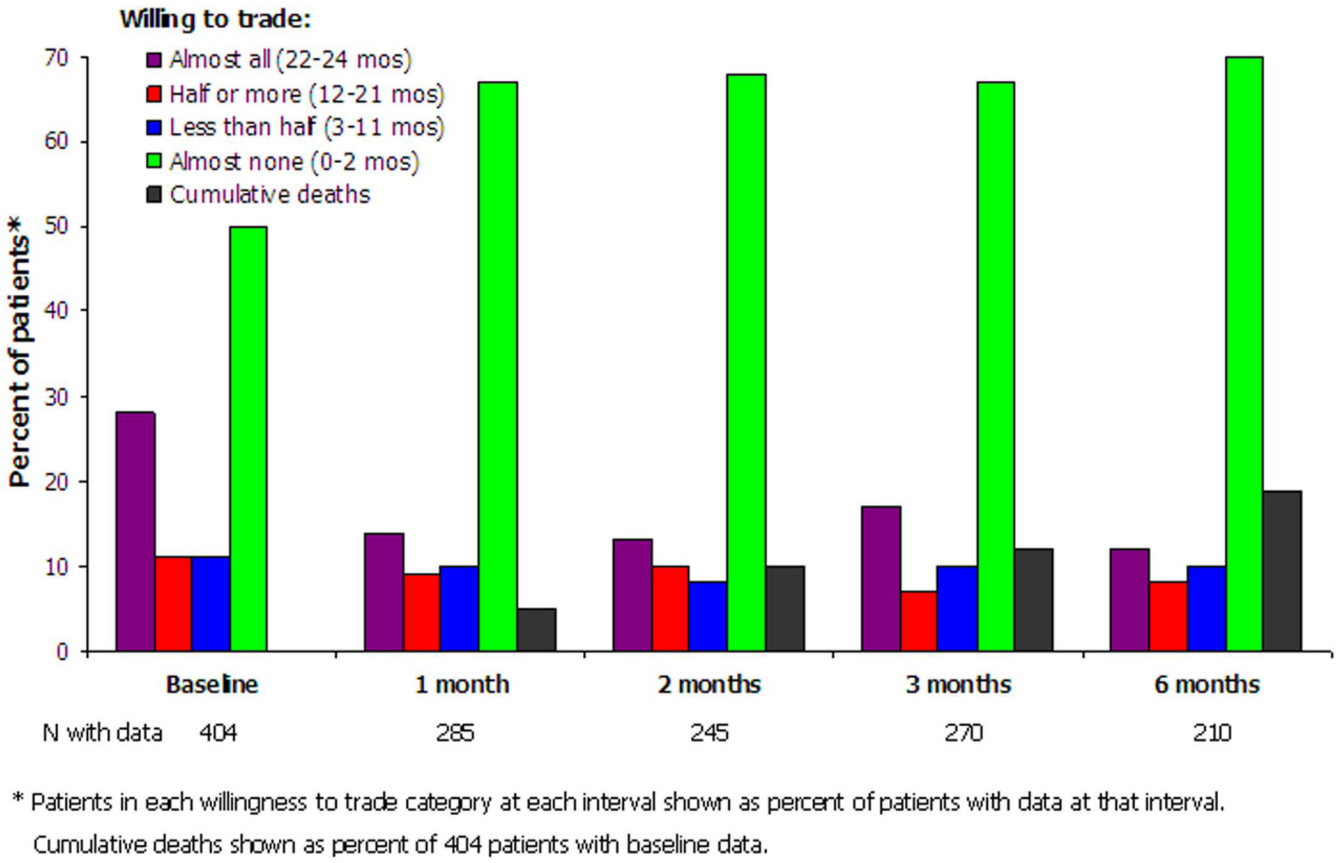


Figure 1. Bimodal Distribution of Patient Preferences

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, 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 four ranges for group description and analysis of major changes.



* Patients in each willingness to trade category at each interval shown as percent of patients with data at that interval.
Cumulative deaths shown as percent of 404 patients with baseline data.

Figure 2. Changing Patient Preferences After Hospital Discharge

Bar graph indicates proportions of patients in each time trade-off group at different times after hospital discharge. The number of patients responding for each interval is shown below. The cumulative number of patients dying by the end of each interval is shown in the black bars. Definitions of intervals are as in previous tables and figures.

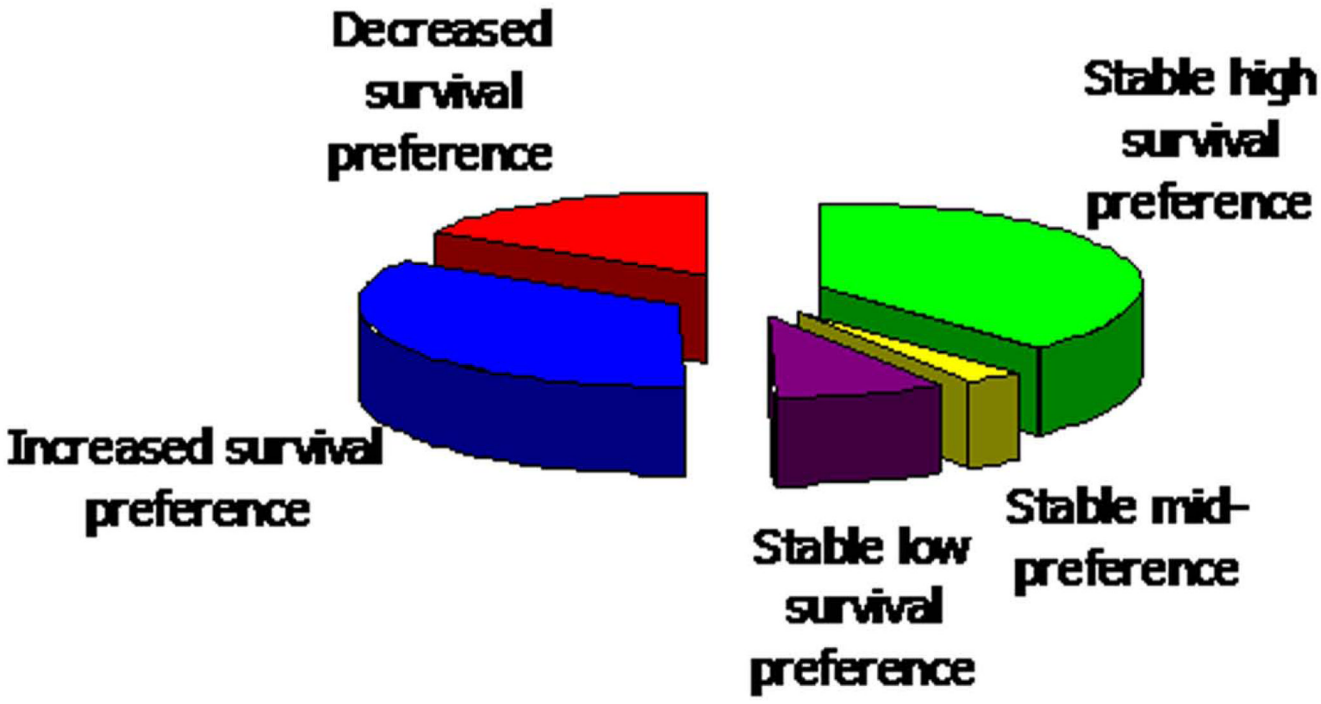


Figure 3. Stability of Survival Preference

Pie graph showing 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 1. Patients remaining in the highest survival preference are “stable high”, those remaining in the lowest survival preference are “stable low”. Patients remaining in one of the two other time-trade off groups are “stable mid-preference”. While the majority of patients demonstrated no change in preference, more patients described an increase than a decrease in preference for survival.

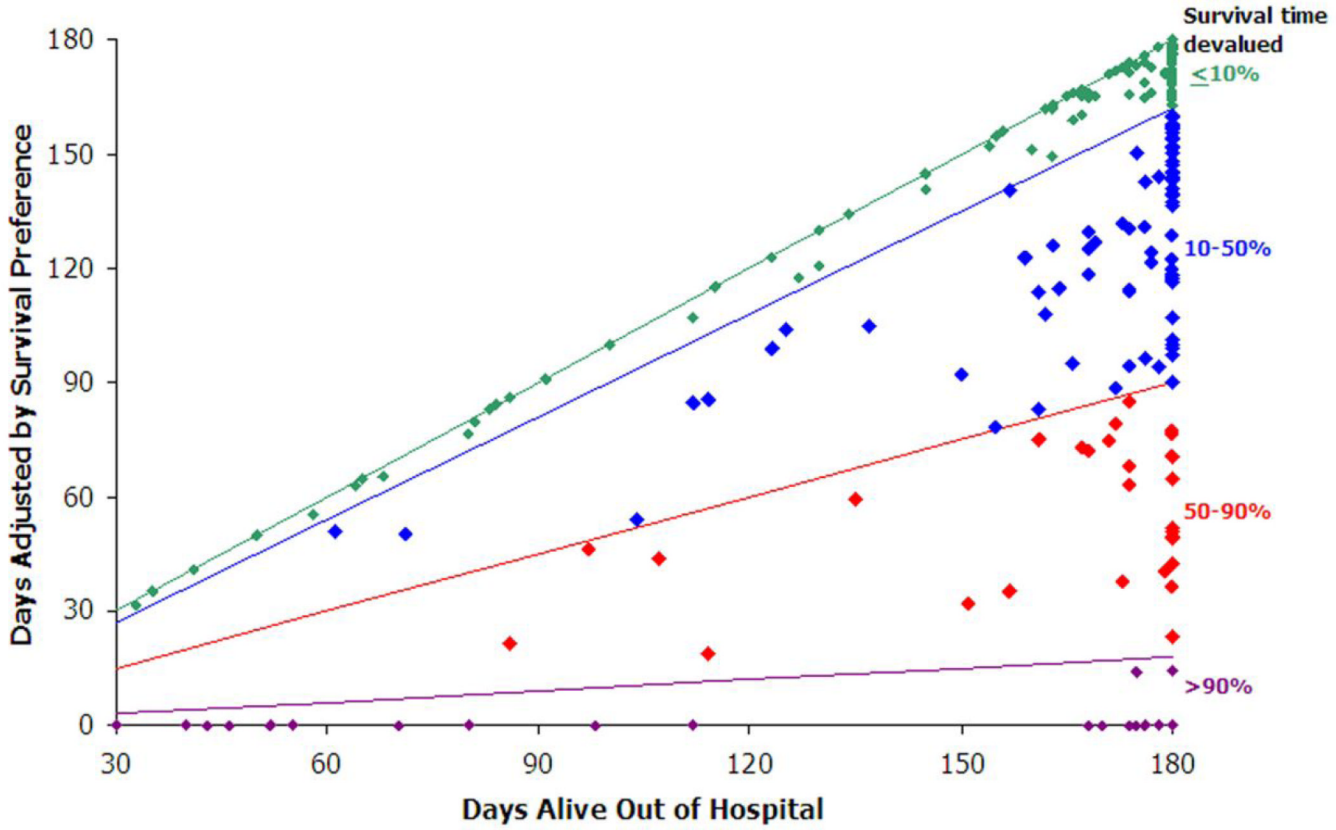


Figure 4. Patient-Preferred Survival

Days alive adjusted by time trade-off. The x–y plot compares for each patient the actual survival days during 6 months to the survival days adjusted for the survival preference described by the patient during each interval (see text). 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 more than 90% of their remaining days in order to feel better, compared to 6% of patients surviving all 180 days.

Table 1

Characteristics of patients grouped by baseline time trade-off levels

	Willing to trade almost all time 22–24 months (N=112)	Willing to trade half or more time 12–21 months (N=45)	Willing to trade less than 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, %	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, 1199)	575 (344, 1395)	681 (223, 1107)	528 (159, 1089)
6-min walk, ft*	196 (0, 556)	364 (0, 650)	520 (150, 981)	371 (0, 840)

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

* Difference in 6-minute walk across groups($p<0.003$).

Table 2

Characterization of patients with missing time trade-off data at baseline or follow-up

Baseline factor	Patients without baseline TTO data (N=29)	Patients with baseline who survived without follow-up TTO (N=62)	Patients with baseline and TTO at 3 and/or 6 months (N=287)
Male, %	79	68	75
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, 1952)	585 (257, 1042)	511 (193, 1044)
6-min walk, ft	120 (0, 530)	26 (0, 531)	444 (20, 854)
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)

Median (25th, 75th) unless otherwise indicated.

Table 3

Improvement in functional parameters by 3 months in relation to changing preferences

Functional parameter of improvement, indicated by + for all measurements except MLHF, in which lower scores reflect less limitation	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 86 + 50 = 136	P value
Patient global health visual analog score	+19 (28)	+8 (27)	95	0.126
Breathing visual analog score	+12 (31)	+9 (22)	49	0.56
Freedom from worst symptom visual analog score	+25 (31)	+8 (23)	92	0.0065
MLHF	− 22 (23)	−10 (25)	94	0.014
6-minute walk, ft	+426 (403)	+329 (546)	59	0.27
Improvement in at least 2 of above*	83%	59%	96	0.011

Table entries are mean (standard deviation) except last row. P-values from Wilcoxon rank sum tests except last, from likelihood ratio chi square.

*Defined as increase at least 10 for visual analog scores, decrease at least 5 for MLHF, increase at least 50 feet for walk.