Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 47, No. 8, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.11.069

A Comparison of the Effects of Carvedilol and Metoprolol on Well-Being, Morbidity, and Mortality (the "Patient Journey") in Patients With Heart Failure

A Report From the Carvedilol Or Metoprolol European Trial (COMET)

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OBJECTIVES This study was designed to investigate the loss of well-being, in terms of life-years, overall and in patients randomized to metoprolol versus carvedilol in the Carvedilol Or Metoprolol European Trial (COMET).

BACKGROUND The ultimate objectives of treating patients with heart failure are to relieve suffering and prolong life. Although the effect of treatment on mortality is usually described in trials, the effects on patient well-being throughout the trials' courses are rarely reported.

METHODS A total of 3,029 patients randomized in the COMET study were included in the analysis. "Patient journey" was calculated by adjusting days alive and out of hospital over four years using a five-point score completed by the patient every four months, adjusted according to the need for intensification of diuretic therapy. Scores ranged from 0% (dead or hospitalized) to 100% (feeling very well).

RESULTS Over 48 months, 17% of all days were lost through death, 1% through hospitalization, 23% through impaired well-being, and 2% through the need for intensified therapy. Compared with metoprolol, carvedilol was associated with fewer days lost to death, with no increase in days lost due to impaired well-being or days in hospital. The "patient journey" score improved from a mean of 54.8% (SD 26.0) to 57.4% (SD 26.3%) ($p < 0.0068$).

CONCLUSIONS Despite treatment with beta-blockers, heart failure remains associated with a marked reduction in well-being and survival. Loss of quality-adjusted life-years through death and poor well-being seemed of similar magnitude over four years, and both were much larger than the loss that could be attributed to hospitalization. (J Am Coll Cardiol 2006;47:1603–11)

Ideally, a treatment for heart failure (HF) should reduce mortality, prevent or shorten hospitalization, improve well-being, and reduce the need for intensification of treatment. However, these are competing outcomes. In clinical trials, an excess of death in one group may reduce non-fatal morbid events and days in hospital because patients are exposed to less overall time at risk (1). Moreover, treatments that reduce mortality often selectively exert a greater absolute reduction in mortality amongst the sickest patients, who report more symptoms and have a higher rate of morbid events. This will introduce bias into the assessment of non-fatal outcomes, leading to an underestimate of the true effects of therapy (1,2). An effect of treatment on symptoms may also be obscured if there is more intensification of treatment for symptoms in one group (1).

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One way around the inadequacy of single measures to describe the effects of treatment is to measure clinical composite outcomes (1–3), but these can be difficult to interpret and misleading (2). Time to first-event analysis for death or hospitalization has become popular because it increases the event rate and therefore potentially increases the power of the study, thus enabling the detection of smaller differences in effect or allowing the study size to be

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Manuscript received June 28, 2005; revised manuscript received October 17, 2005, accepted November 16, 2005.

JACC Vol. 47, No. 8, 2006
April 18, 2006:1603–11

Abbreviations and Acronyms

COMET = Carvedilol Or Metoprolol European Trial
HF = heart failure
NYHA = New York Heart Association

reduced (4–9). Such composites can be analyzed using conventional survival-type analyses, but ignore all events (including death) after the first event, give preferential emphasis to minor events (because these occur more frequently and therefore usually earlier than major ones), and do not incorporate information on the patients' day-to-day well-being. In such analyses, a brief admission to a hospital with atypical chest pain in the first month carries greater statistical significance than a major stroke or death in the second month. Therefore, such composite measures imperfectly reflect the patients' experience of their illness and its modification by therapy.

An alternative way to combine data is to use all the available information to produce a composite of days alive and out of hospital adjusted for well-being and the need for intensification of therapy (1,10). This has been termed the "patient journey" (1) and is close in concept to quality-adjusted life-years (11), a tool commonly used for health economic analyses. This type of analysis can be used to evaluate both the effects of treatment and the unmet needs of patients.

The Carvedilol Or Metoprolol European Trial (COMET) (6,12,13) compared the effects of carvedilol and metoprolol on morbidity and mortality. Serial data on symptoms, patient well-being, and hospitalization were collected, in addition to mortality, allowing the "patient journey" and its individual components to be assessed in patients receiving contemporary therapy for the first time in a large study.

METHODS

The COMET study was an international, multi-center, randomized (1:1), double-blind, parallel group trial comparing the effect of carvedilol and metoprolol tartrate on morbidity and mortality in patients with chronic HF. Detailed descriptions of the study design, baseline characteristics, and results have been published (12).

Patients. The main inclusion criteria were the presence of chronic symptomatic New York Heart Association (NYHA) functional class II to IV HF, left ventricular ejection fraction ≤35%, at least one cardiovascular hospitalization during the previous two years, receiving stable HF treatment with angiotensin-converting enzyme inhibitors for at least four weeks unless contraindicated, and receiving treatment with diuretics (≥40 mg of furosemide or equivalent) for at least two weeks. Patients with a contraindication to a beta-blocker, uncontrolled hypertension, major valvular disease, or a major vascular event or ventricular arrhythmia within the previous two months were excluded.

The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. The relevant, local ethics review boards approved the protocol. Written informed consent was obtained in all patients before enrolment.

Trial procedures. At randomization, eligible patients (3,029) were assigned to receive either carvedilol (3.125 mg twice daily) or metoprolol tartrate (5 mg twice daily). The dose of each beta-blocker was increased to the target dose of carvedilol (25 mg twice daily) or metoprolol (50 mg twice daily) at two weekly intervals.

During the maintenance phase, patients were assessed every four months. At each assessment, patients were invited to report the severity of their breathlessness, fatigue, and overall well-being using a simple five-point scale. Investigators recorded NYHA functional class and current HF medication. The reasons for and dates of admission and discharge were recorded for all hospitalizations and the date of death if it occurred.

Methodology for construction of the "patient journey." The "patient journey" comprises four major components that are relevant to the patients' experience: longevity, days in hospital, well-being or symptoms, and the need for intensification of diuretic therapy to control symptoms (13). Assigning an arbitrary value to each component allows an overall "patient journey" score to be calculated for each patient. Each individual patient's "journey" should be of equal potential duration to other patients with whom their outcome is being compared. Thus, outcome over one year, two years, three years, and four years is described. A large number of patients were not followed for more than four years, and therefore scores beyond four years were not calculated.

Death and hospitalization. Patients were assigned a score for each day alive and out of hospital. On the day that the patient died and for every day thereafter, the patient was assigned a score of zero. Days spent in hospital were also assigned a zero score.

Well-being and symptoms. The primary analysis of interest was conducted using a five-point scoring system asking patients how well they felt every four months. Investigators were required to ask patients, "On a scale of one to five, where one is very good and five is very poor, how have you been feeling over the past week?" and instructed to take the answer given without trying to interpret or modify it. A score of 100% was assigned for each day alive and out of hospital if the patient reported feeling very good ("well-being" score 1). The score was reduced by 20% for each decrement in the patient-reported score down to a lowest potential score of 20% ("well-being" score 5). Patients were assumed to have a health state that was the average of the assessment at the beginning and end of the four-month period (effectively a "running mean"), with zero scores for days in hospital. If a patient was in hospital at the four-month assessment, the actual scored assessment was still used to calculate average "well-being." If no assessment of

well-being was reported at this time, the patient was assumed to be in the worst health state. If a patient died of worsening HF during any follow-up period, it was assumed that they were in the worst health state on the day of death, and this was used to calculate average health state. If the patient died of other causes (mainly sudden death), they were assumed to be in the same health state on the day of death as that last recorded. If a scheduled measurement of well-being was missed, average health state could be calculated using the next measurement and averaging over a longer period. This included deaths.

A secondary analysis was performed using NYHA functional class based on comparative data with a visual analogue scale, the Ladder of Life questionnaire, used in the Studies Of Left Ventricular Dysfunction (SOLVD) study (14) and rebased so that patients in NYHA functional class I were deemed to have the best possible score (i.e., 100%). Thus, NYHA functional class I was ranked 100% (71% actual in SOLVD), NYHA functional class II 86% (61% actual), NYHA functional class III 73% (52% actual), and NYHA functional class IV 66% (47% actual).

Further analyses were conducted using different assumptions about patient well-being reflecting either the view that surviving with poor well-being has a low value ("well-being" scored as 100%, 90%, 70%, 30%, and zero) or that survival regardless of health state has a high value ("well-being" scored as 100%, 90%, 80%, 70%, and 60%). These analyses allow the trial result to be viewed from different patient perspectives. It is essential, in order to comprehend the utility of the "patient journey," to understand that it is the view of future patients not involved in the trial (external perspective) rather than the "historical" patients who participated in the trial who should judge which values to assign to scores, because each individual patient is different and the patients to whom the data will be applied will rarely be the individuals who participated in the study. Also, the value ascribed to living in different health states may change within an individual patient over time.

Intensification of therapy. There are many reasons treatment might be increased in patients with HF (1). Digoxin may have been given for atrial fibrillation. Angiotensin-converting enzyme inhibitor dose may have been increased and aldosterone antagonists introduced because of a perceived prognostic benefit rather than a change in the patient's status. On the other hand, there are few reasons to increase the dose of a diuretic other than for worsening symptoms or signs, and the need for higher doses of diuretics indicates a worse prognosis. Addition of a loop diuretic to a thiazide or vice versa or an increase in furosemide or equivalent (furosemide 40 mg = bumetanide 1 mg = torasemide 10 mg) by both >40 mg/day and by 50% was taken as evidence of a need for intensified diuretic therapy. Changes in diuretic therapy were assessed only at four-month intervals. If treatment had been increased, the patient was assumed to be one rank worse than actually scored at that time point, unless already in the worst rank, in which case no penalty was applied. This effectively assumes that change in therapy occurred at the midpoint of the interval assessed. Temporary changes in therapy that did not persist until a four-month assessment were ignored. A penalty for increased diuretic therapy could be incurred only once, to allow for the fact that some clinicians might titrate diuretic therapy gradually whereas others will make more radical changes. Patients who had diuretic therapy reduced to baseline levels lost any imposed penalty. Reduction of diuretics to below baseline levels did not lead to improved scores in this analysis.

Statistical design and analysis. The co-primary end points of the study were all-cause mortality and the composite end point of all-cause mortality or all-cause hospitalization. All four individual components of the "patient journey" were secondary end points, including NYHA functional class, number and duration of hospitalizations, need for increased diuretic therapy, and death. The concept of the "patient journey" outcome measure evolved during the course of the study, and details were published before unblinding of the study but were not a pre-specified outcome (1). Accordingly, statistical analysis of this outcome should be considered exploratory to assist in the design and interpretation of future studies. All randomized patients were included in the

Table 1. Baseline Characteristics

	Carvedilol (n = 1,511)	Metoprolol (n = 1,518)
Age (yrs)	61 ± 11	62 ± 11
Gender (% male)	79	80
Systolic BP (mm Hg)	126 ± 19	126 ± 20
Diastolic BP (mm Hg)	77 ± 11	77 ± 11
Heart rate (beats/min)	81 ± 13	81 ± 14
NYHA functional class		
II	48	49
III	48	47
IV	3	4
Aetiology CHF*		
Ischemic heart disease	51	54
Hypertension	18	18
Dilated cardiomyopathy	44	44
Previous valve surgery	3	2
LVEF	26 ± 7	26 ± 7
Diabetes	24	24
Stroke	7	7
Atrial fibrillation/flutter	21	19
Concomitant medication at randomization		
Diuretics†	99	99
ACE inhibitors†	92	91
Angiotensin receptor antagonists	6	7
Digitalis	61	58
Antiarrhythmics	13	12
Nitrates	32	32
Aldosterone antagonists	11	11
Anticoagulants	48	44
Aspirin	35	39
Lipid-lowering agents (statins)	20	22

*More than one answer possible; †Inclusion criteria. Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; BP = blood pressure; CHF = chronic heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

analysis using the intention-to-treat principle. It was planned that all patients would be followed to the end of the study, even after permanent cessation of study treatment or after heart transplantation. Some patients were lost to follow-up or withdrew consent. These patients were censored at the last known date of contact or date of withdrawal from the trial. Using the methods in this study, a complete "patient journey" over four years could be calculated for 97% of patients.

A descriptive analysis to show how key patient characteristics affected the "patient journey" including gender, age above or below 65 years, NYHA functional class II, III, or IV, and left ventricular ejection fraction above or below 25% was conducted. For mortality, Kaplan-Meier survival estimates were calculated and differences assessed using Cox proportional hazard models. Differences in continuous variables were assessed by *t* tests and by the chi-square test for categorical data. For each patient, a proportion of days lost in each interval was calculated, and differences between the treatment groups were assessed using *t* tests.

RESULTS

Of 3,029 patients, 1,511 were assigned to treatment with carvedilol and 1,518 to metoprolol. The mean study duration was 58 months. Five patients were lost to follow-up and 28 patients, one of whom underwent heart transplantation, withdrew their consent during the course of the study. Twenty-eight patients in the carvedilol group and 27 patients in the metoprolol group underwent heart transplantation. The two treatment groups were similar with respect to baseline characteristics and concomitant therapies at entry (Table 1).

Mortality. A total of 512 deaths were recorded in patients assigned to carvedilol, compared with 600 deaths in those assigned to metoprolol (hazard ratio of 0.83; 95% confidence interval 0.74 to 0.93, p = 0.0017) (Table 2). Overall, 5.4% of days of follow-up (59,954 days) were lost through death in the first year, increasing cumulatively to 17.0% (751,003 days) by the end of the 4th year.

Hospitalization. The number of hospitalizations and hospital days was similar during treatment with carvedilol and metoprolol (Table 2). During the first year, patients spent 1.8% of study days (20,220 days), and cumulatively over four years, 1.4% of study days in hospital (63,428 days) or 1.7% of days alive.

Well-being and NYHA functional class. The baseline distribution of well-being scores are shown in Figure 1, according to NYHA functional class, age, and gender.

Table 2. Cumulative Distribution and Reason for Days of Life Lost Over 4 Years

	Carvedilol Days	% Loss	Metoprolol Days	% Loss
1 year				
Potential days	551,515		554,070	
Days lost to				
Death	28,292	5.1	31,662	5.7
Hospitalization	9,738	1.8	10,482	1.9
Impaired well-being	151,115	27.4	153,526	27.7
Diuretic adjust	9,684	1.8	10,706	1.9
Total life lost	198,829	36.1	206,376	37.2
2 years				
Potential days	1,103,030		1,108,140	
Days lost to				
Death	99,626	9	111,623	10.1
Hospitalization	18,043	1.6	18,043	1.6
Impaired well-being	281,565	25.5	287,901	26.0
Diuretic adjust	22,746	2.1	24,104	2.2
Total life lost	421,979	38.3	441,671	39.9
3 years				
Potential days	1,654,545		1,662,210	
Days lost to				
Death	209,000	12.6	234,139	14.1
Hospitalization	25,234	1.5	25,082	1.5
Impaired well-being	398,673	24.1	410,428	24.7
Diuretic adjust	36,352	2.2	37,857	2.3
Total life lost	669,259	40.4	707,506	42.6
4 years				
Potential days	2,206,060		2,216,280	
Days lost to				
Death	349,983	15.9	401,020	18.1
Hospitalization	31,658	1.4	31,770	1.4
Impaired well-being	508,431	23.0	517,218	23.3
Diuretic adjust	49,462	2.2	51,138	2.3
Total life lost	939,534	42.6	1,001,147	45.2

Well-being score reported is base case. A 1% difference reflects about 22,000 days difference over 4 years, or about 15 days of full health per patient.

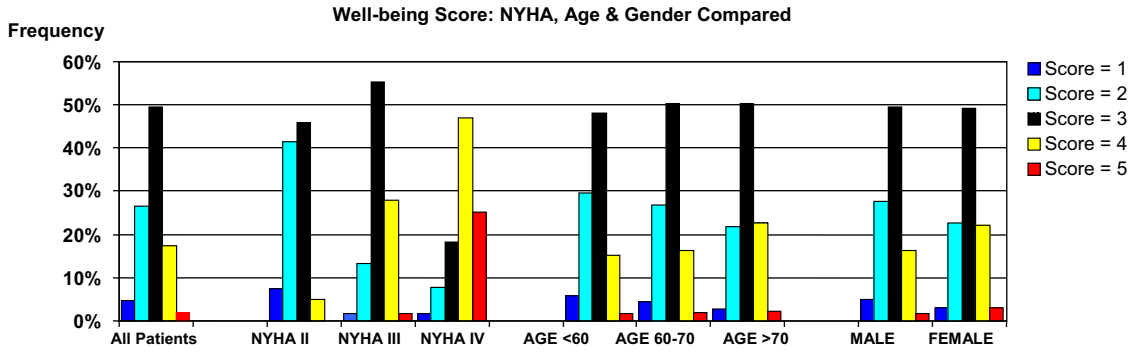

Figure 1. Distribution of patients' scoring of well-being on a scale of 1 (very good) to 5 (very poor) according to age, gender, and investigator-determined New York Heart Association (NYHA) functional class.

Patients with higher NYHA functional class and greater age generally had worse scores for well-being, but the distribution of scores was similar in men and women.

During the first year, patients spent 166,568 days in well-being state 4 or 5 (16% of days alive) and 383,391 days (37%) in NYHA functional class III or IV. Over four years, 616,608 days (17% of days alive) were spent in well-being state 4 or 5 and 1,272,527 days (35%) were spent in NYHA functional class III or IV (Table 2). Overall, 28% of days (304,641 days) were lost through impaired quality of life during the first year of follow-up and, cumulatively, 23% (1,025,649 days) during four years of follow-up using the base-case well-being score (Table 2). If only days alive are included, then 28% were lost to impaired well-being during four years of follow-up.

Adjustment for increasing diuretic requirement. Adjustment of quality-of-life scores because of increasing diuretic requirements caused the loss of 1.8% (20,390 days) of days in the first year and 2.3% (100,600 days) cumulatively over four years using the well-being score and 1.0% (10,537) and 1.2% (53,877 days) using scores based on NYHA functional class (Table 2). No differences between carvedilol and metoprolol were identified.

Overall composite score. Overall, patients lost 37% of days of life (405,205 days) in the first year and 44% (1,940,680 days) over four years after adjustment for well-being (base case) and treatment (Table 2). The composite outcome reflected mostly loss of quality of life initially, but mortality became a more important component with long-term follow-up (Fig. 2). Days in hospital and adjustment of health state for increases in diuretics made a small contribution to the composite outcome. If scores for NYHA functional class were substituted for the well-being score, days of life lost were 24% (266,072

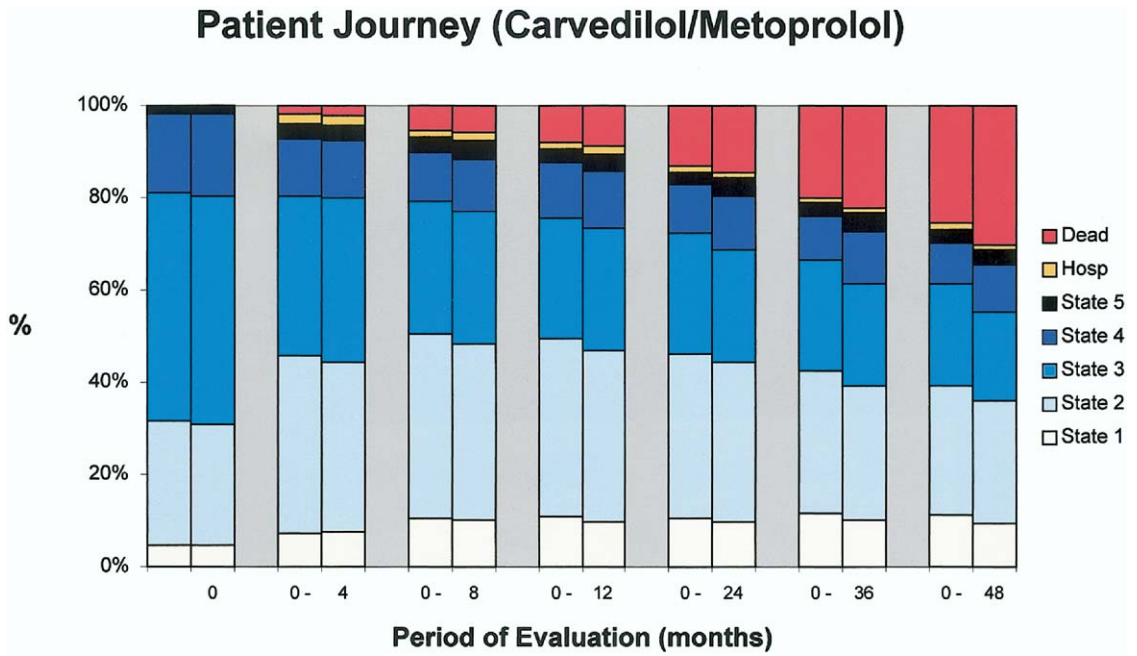

Figure 2. Cumulative amount of time spent in each health state during different follow-up periods expressed as a proportion of potential days follow-up, alive or dead. The difference between interventions was significant ($p = 0.0068$). For the base case, a score of 100% was assigned for each day alive and spent out of hospital if the patient reported being very well ("well-being" score 1) and was reduced by 20% for each decrement in the patient-reported score down to a lowest potential score of 20% ("well-being" score 5).

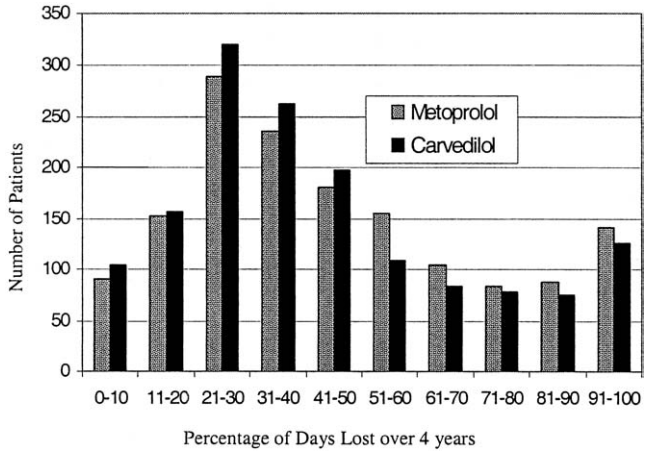

Figure 3. Distribution of percentages of notional days of life lost using the "patient journey" score. The best possible score is 0% loss (surviving 4 years with best well-being state, without increased need for diuretic therapy, hospitalization, or death). Poor scores may reflect early death, persistently poor well-being, or prolonged periods of hospitalization, or any combination of such events. Data shown use the base-case set of scores for well-being. Note the shift to the left in scores among patients randomized to carvedilol compared to metoprolol ($p = 0.0068$).

days) in the first year and 33% (1,437,351 days) over four years.

Overall, compared to metoprolol, carvedilol reduced the total number of days lost over one year from 206,376 (37%) to 198,829 (36%) in the first year and from 1,001,147 days (45%) to 939,534 (43%) over four years using base-case well-being scores ($p = 0.0068$) (Fig. 2). However, mean differences reflect the heterogeneity in outcome poorly. The distribution by centiles of individual patient outcomes for patients assigned to metoprolol and carvedilol is shown in Figure 3. Carvedilol shifted the distribution of outcomes favorably ($p = 0.0068$). From this distribution, it can be calculated that one in every eight patients switched from metoprolol to carvedilol would have an absolute improvement of 10% in their "patient journey" score over four years, notionally equivalent to an extra five months of full health. Figure 4 summarizes the effects of different assumptions about the value that should be assigned to well-being other than the base-case assumption. One set of values (designated "well-being") reflects the view that survival with poor well-being is of low value, another (designated "life") the view that survival even with poor well-being has a high value. Finally, a set of assumptions based on NYHA functional class reported in the SOLVD trial is given. These show the sort of variation and variation in difference between carvedilol and metoprolol that might be expected. The score was unaffected by the inclusion or exclusion of the few patients who received heart transplants.

Outcomes in subgroups (Fig. 5). Men and women had similar overall "patient journey" scores, although loss through death tended to be greater in men and loss of well-being greater in women. Older patients had worse scores, owing entirely to a higher mortality. Patients with more severe symptoms at baseline also had worse overall scores, but mainly owing to higher mortality. Patients initially in NYHA functional class IV lost 39% of follow-up days to death, 2% to hospitalization, and 23% to poor well-being over four years, whereas patients initially in NYHA functional class II lost 12%, 1%, and 21% respectively. Patients with lower left ventricular ejection fraction had slightly worse scores owing to a higher mortality, but not poorer well-being. Carvedilol appeared superior to metoprolol in all groups of patients studied (Fig. 6).

DISCUSSION

This analysis of the COMET study suggests that a composite outcome measure, such as the "patient journey," provides a powerful, comprehensive measure of the benefits of therapy and the still-unmet needs of patients with HF. Unlike conventional composite measures, it uses a large amount of the available data and not just one potentially misleading event. It is also a more robust measure of the effects of therapy on well-being because it does not depend on a single evaluation that may be unrepresentative of the overall effect of treatment and because it does not require arbitrary conventions to deal with values that are lost through the patient's death.

Death and patient-evaluated well-being appear to be the major factors that drive this outcome measure, whereas hospitalization and adjustment attributable to the need for intensified therapy make relatively small contributions, at least in the types of patients enrolled in the COMET study. Clinical trials have emphasized the importance of reducing mortality but have placed less emphasis on improving patients' symptoms, and have often used events such as hospitalization, myocardial infraction, or stroke as a surrogate measure of symptoms or disability. Even though we

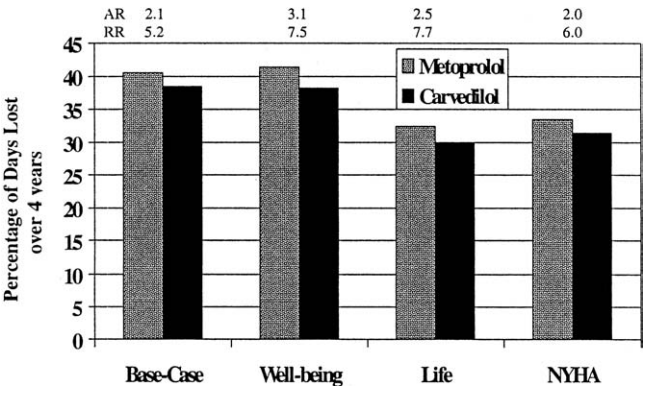

Figure 4. Comparison of percentage of days alive lost due to poor well-being in patients randomized to carvedilol or metoprolol using four different sets of scores. Note that patients receiving carvedilol lived longer, and therefore potential days lost to poor well-being while receiving carvedilol were higher than for metoprolol. "Base case" represents well-being scores of 100, 80, 60, 40, or 20. "Well-being" reflects the view that survival in a poor health state has low value (100, 90, 70, 30, 0). "Life" reflects the view that survival regardless of health state has high value (100, 90, 80, 70, 60). "NYHA" reflects scores derived from Glick et al. (14) (100, 86, 73, 66). AR = absolute reduction with a 1% difference reflecting about 200,000 days in study or about 15 days per patient; RR = relative reduction.

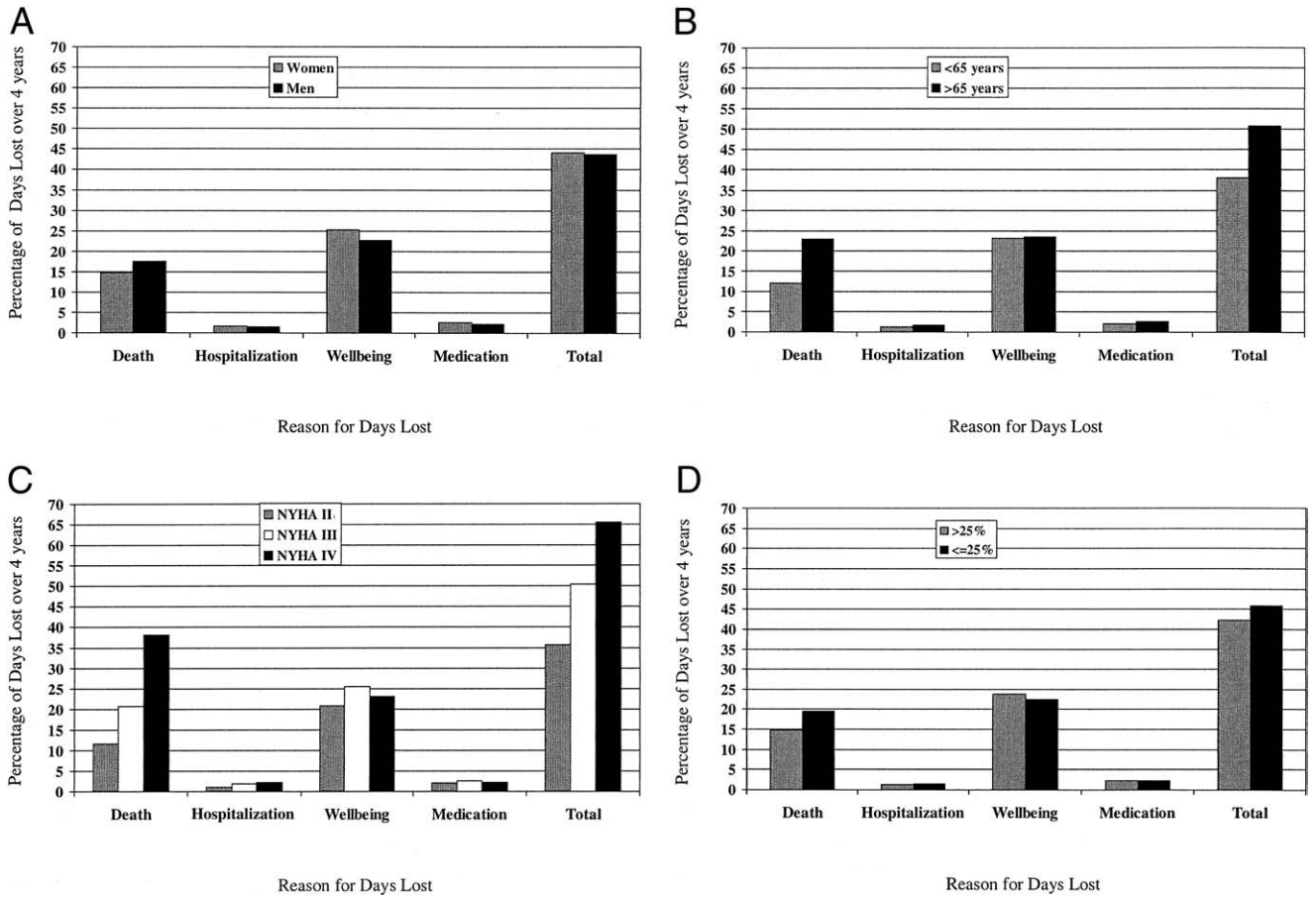

Figure 5. Days lost, overall and by component of the "patient journey," in subgroups of patients according to gender **(A)**, age **(B)**, New York Heart Association (NYHA) functional class **(C)**, and left ventricular ejection fraction **(D)**.

valued days lost through hospitalization the same as death, which some may consider too severe, it added relatively little to the total loss of life-days. Even though hospitalization may be a very distressing event, most patients recover. It is more relevant to measure symptoms and disability rather than to impute them from sparse events. This analysis shows that simple, serial direct measures of patient well-being are feasible. This study also emphasizes that improving patient well-being is an important unmet patient need and goal of therapy that has not been well reported in large outcome studies, with few exceptions (7,15).

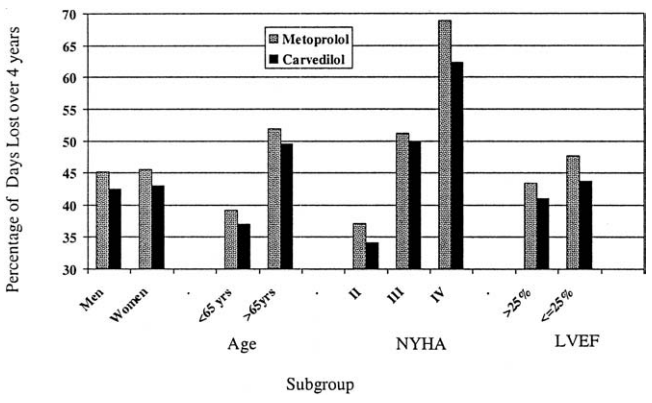

Figure 6. Overall days lost in subgroups of patients according to age, gender, New York Heart Association (NYHA) functional class, and left ventricular ejection fraction (LVEF) in patients randomized to carvedilol or metoprolol.

Compared to metoprolol tartrate, carvedilol reduced the total days lost. This effect was mostly due to increased longevity. Metoprolol tartrate has previously been shown to improve well-being after myocardial infarction (10) and in patients with HF and dilated cardiomyopathy (16), indicating that the effect of carvedilol was in addition to that of an active control. Overall, there was no difference between treatments in loss of days to hospitalization or the need for intensified therapy. Thus, carvedilol did not increase the burden of illness during the period that it extended life.

Quality-adjusted life-years are widely used as a measure of the utility of treatment in health economic analyses. The "patient journey" outcome measure is a similar concept, but also incorporates key health-economic data such as the time spent in hospital. Some might desire a more formal and lengthy tool for the assessment of well-being. However, obtaining complete records repeatedly can be difficult using many quality-of-life tools (15). We opted for a simple tool that could be obtained reliably, at relatively frequent intervals, and without exhausting the patience of investigator or patient. Frequent, repetitive assessment avoids undue

weight being given to solitary events, such as an accident, bereavement, the weather, or a visit from a friend, which may have relatively short-lived effects on how patients feel. Validation of the patient well-being score against more formal quality-of-life instruments would be desirable, but quality of life and well-being are simple, subjective measures. More complex means of assessment are mainly targeted at identifying *why* quality of life is impaired, which is of secondary importance in the context of a large randomized controlled study.

Patient well-being scores were related to NYHA functional class, as might be anticipated (13), although the relationship was not perfect, as has been shown in other trials (17,18). The NYHA functional class is assigned by an investigator and reflects their view of the patient's functional capacity, which may be biased by knowledge about cardiac function and physical frailty as well as the need to fulfill entry criteria for clinical trials. Patient well-being score reflects the patient's view of their symptoms and health and will be modified by the patient's emotional state and the degree to which they have adapted to their illness and symptoms. It is therefore not surprising that there is only a moderate relationship between these scores.

The estimated loss of quality of life by using NYHA functional class was less than that suggested by patient well-being score. This mainly reflected the values attached to the different scoring systems rather than differences in the score assigned. Thus the worst NYHA functional class was valued as 66% of full quality of life, versus a value of only 20% for the poorest well-being score. However, regardless of which measure was used, the pattern of results was similar. Assigning a numerical value to an indicator of well-being or quality of life is arbitrary, and different assumptions can markedly alter the "amount" of life lost owing to poor health compared with that lost through death. However, we used a range of assumptions to reflect different patient-views of the relative importance of survival versus quality of life that allows the trial data to be valued from the perspective of patients, carers, and physicians who are deciding on the utility of the intervention for their own future or their patients.

Despite worse well-being scores among patients with more severe HF at baseline, overall loss of days owing to poor well-being was remarkably similar in patients with NYHA functional classes II, III, and IV. This reflects the fact that overall loss of well-being reflects both the severity of disease and the duration of exposure. This suggests that the "patient journey" is best suited to assessing treatments that alter both well-being and prognosis. This outcome measure is likely to be less robust when used to assess treatments for HF that reduce only mortality. If only mortality is considered, the patient effectively counts as 0% if dead and 100% if alive, whereas when using the "patient journey" relatively few days alive are scored as 100%.

Many refinements could be added to the model, including the validation of simple instruments to measure well-being, formal measurement of quality of life in either a subgroup of patients or on all patients on a few occasions, and the application of discounting, so that life in the early part of the trial is valued more highly. None of these was prospectively planned in this study, but they could be incorporated into future studies.

In conclusion, the proposed outcome measure, "patient journey," appears to be a useful single measure to assess the effects of treatment on symptoms, morbidity, and mortality. The concept would benefit from the use of formal validation of the well-being scores used in this study or the use of an already validated tool. "Patient journey" is improved by carvedilol compared to metoprolol tartrate, mainly owing to a reduction in mortality but, importantly, the mortality benefit did not result in more people staying alive in a very poor health state. It is clear that there is still much room for improvement in the treatment of HF.

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