Cost-Effectiveness Analysis of Long-Term Moderate Exercise Training in Chronic Heart Failure

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The purpose of this study is to perform a cost-effectiveness analysis of long-term moderate exercise training (ET) in patients with stable chronic heart failure. In particular, the study focuses on the survival analysis and cost savings from the reduction in the hospitalization rate in the exercise group. In the past 10 years, ET has been shown to be beneficial for patients with stable class II and III heart failure in many randomized clinical trials. However, the cost-effectiveness of a long-term ET program has not been addressed for outcomes related to morbidity/mortality end points or health care utilization. We examined the cost-effectiveness of a 14-month long-term training in patients with stable chronic heart failure. The estimated increment cost for the training group, $3,227/patient, was calculated by subtracting the averted hospitalization cost, $1,336/patient, from the cost of ET and wage lost due to ET, estimated at $4,563/patient. For patients receiving ET, the estimated increment in life expectancy was 1.82 years/person in a time period of 15.5 years, compared with patients in the control group. The cost-effectiveness ratio for long-term ET in patients with stable heart failure was thus determined at $1,773/life-year saved, at a 3% discount rate. Long-term ET in patients with stable chronic heart failure is cost-effective and prolongs survival by an additional 1.82 years at a low cost of $1,773 per/life-year saved.

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In the past 10 years, the beneficial effects of exercise training (ET) for class II and III patients with stable heart failure have been firmly established by several randomized clinical trials.[1–5] ET programs of various intensities resulted in significant improvements in exercise capacity, reduced sympathetic drive, and increased vagal tone.[1–5] Moreover, recent investigations showed improvements with exercise in endothelial function and skeletal muscle function.[6–10] However, the cost-effectiveness of an ET program has not been addressed for outcomes related to morbidity/mortality end points, and it has not been conducted for purposes of long-term health care utilization. With the advent of new and costly interventions, such information is crucial for the development of cardiac rehabilitation centers for patients with heart failure. Therefore, the purpose of the present study was to perform a cost-effectiveness analysis based on the efficacy results of the largest randomized trial.[1] Specifically, this study focuses on the survival analysis and the cost savings from the reduction in the rate of hospitalizations in the exercise group.

METHODS

To determine the cost-effectiveness of a 14-month-long moderate ET in heart failure, published results from a recent randomized controlled clinical trial were used.[1] A standard cost-effectiveness analysis was performed[11] and the cost-effectiveness ratio, expressed in dollars per year of life saved, was calculated. A discount rate of 3% was selected and applied to costs and consequences to address subjects' time preference for the future costs and benefits.[11] In our analysis, costs referred to the cost of exercise program, wage lost due to attending exercise program, and the cost of hospitalization due to heart failure. We did not include travel expenses for attending the exercise program, and we did not include indirect costs such as loss of income due to disability. Effectiveness was measured as the incremental life expectancy attributable to ET. Other health outcomes such as pain, disability, and physical functions were not included. A 14-month time frame was used for the ET program and a cohort population of class II and III heart failure patients between the ages of 55 and 64 years was developed.

Determining effectiveness: Effectiveness of the ET program was measured as the increment in life expectancy comparing the training group with the control group in the randomized study. A piece-wise exponential survival model with a constant hazard rate for 2 periods of time (period 1, the training period and the

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TABLE 1 Survival Probabilities*

	Training Group			Control Group		
	m(j) (%)†	h(j)‡	Cumulative Survival (%)§	m(j) (%)†	h(j)‡	Cumulative Survival (%)§
Exercise period and follow-up, $j = 1$	18	0.0001221	82	41	0.0003199	59
10 years after follow-up, $j = 2$	49	0.0001848	42	49	0.0001848	30

*Survival probabilities using the survival model and cumulative survival rates for the training group and the control group. Except for the first period, the daily hazard rates for the training and control groups were assumed to be identical. Compared with the control group, the resulting survival at the end of each period is much higher in the training group.

†Mortality of the *j* period; ‡ daily hazard rate; § at the end of *j* period.

follow-up period; period 2, the first 10 years after the follow-up) was assumed (Table 1). The constant hazard is represented as follows:

$$h(j) = -[\ln(1-m(j))]/t$$

where j = 1, 2, denotes period, m(j) stands for the mortality of *j* period, and t indicates the number of days in the *j*th period. Cumulative survival through *k* days was given by:

$$S(k) = \exp\{-\sum_{i=1}^{k} h(i)\},$$

where h*(i)* denotes the hazard rate of the *i*th day.[12]

In this model, we assumed that the hazard of death after the follow-up period did not depend on the ET program. Survival rates for the 14-month ET and the following 1,214 days of follow-up were derived directly from the randomized study, in which the mortality rates at the end of follow-up were 18% and 41% for the training and control groups, respectively. Survival probabilities after the follow-up period were applied identically to the exercise and control groups. To estimate the survival rates after the 1,214-day follow-up, we calculated the 10-year mortality rates from the National Health and Nutrition Examination–I Epidemiologic Follow-up Survey (1982 to 1986),[13] which established survival data of heart failure for noninstitutionalized adults of all age groups.[14] To generate more comparable estimates for the study subjects in the randomized study, the sex-specific survival rates of ages 55 to 64 were selected and were weighted by the sex ratio in the training and nontraining groups (0.9:0.1, men to women). Also, the survival rates were adjusted upward by 23% based on improvements in chronic heart failure survival resulting from treatment with angiotensin-converting enzyme inhibitors[15–16] introduced after the National Health and Nutrition Examination–I study.[13]

Determining costs in the primary analysis: COST OF EXERCISE TRAINING: The costs were expressed in 1999 dollars for New York City. Equipment, rented space, and salary constitute the direct costs in the primary analysis.

In the randomized trial, ET was performed in 2 phases. Initially, patients exercised 3 times/week for 8 weeks at 60% of peak oxygen consumption. This protocol was followed by a 12-month maintenance program of the same intensity but with only 2 sessions/week. Each session lasted approximately 1 hour, beginning with a warm-up phase of stretching exercises (15 to 20 minutes) followed by 40 minutes of cycling on an electronically braked cycle ergometer.[1] Each person, therefore, went through 128 sessions for a total of 128 hours. In our calculation of costs, we assumed the training program was hospital-based, and the hospital would hire an exercise trainer to supervise the training sessions for a group of 4 patients at a time. The breakdown of the different costs incurred by ET is shown in Table 2. The cardiopulmonary stress test costs $184 including the physician component of interpretation and exercise prescription. Consequently, the overall cost of the exercise program was estimated as $2,054/patient for the 14 months of ET.

COST OF WAGE LOST: Wage lost due to ET was calculated using the published data from the U.S. Census Bureau. In 1998, the median earnings of full-time, year-round workers aged 55 to 64 were $40,654 for men and $26,144 for women. The combined median earning, weighted by the sex ratio in the study population of the original randomized clinical trial[1] was $39,203. Assuming that a person works 2,000 hours/year, the average wage per hour is $19.60. Therefore, the wage lost attributed to 128 hours of ET is $2,509/person. We made the conservative assumption that all persons enrolled in the ET were full-time, year-round workers. We further assumed that patients obtain no utility from exercise. If patients enjoy exercise, this estimate overstates the true opportunity cost of the program.

COST OF HOSPITALIZATION: Delea et al[17] estimated the cost of hospitalization for patients with chronic heart failure using the data from the Health Care Cost and Utilization Project (HCUP-3) National In-patient Sample (Release 1). The HCUP-3 data set contains information from hospital discharge abstracts and summary bills for 6.5 million in-patient stays in >900 community hospitals in the US in 1993. Delea et al[17] used this database to identify all hospitalizations with a principal diagnosis of congestive heart failure. Estimating the cost of each such admission by multiplying total billed charges by the institution-specific cost-to-charge ratio, they then calculated the mean cost and length of stay of all such admissions. All hospitalized patients were assumed to receive admission, discharge, and daily physician visits. The costs of those visits were estimated using national Medicare Part B payment rates.[16] They determined the cost per admis-

TABLE 2 Cost of Exercise Program*

	Cost for Group of 4 Patients		Cost/Patient
	Yearly	128 Hours	(128 sessions)
Salary			
Exercise trainer	$30,000	$1,920	$480
Fringe benefit (29% of salary)	$8,700	$557	$139
Equipment			
4 cycle ergometers (Sensormedics 800S)	$3,200	$205	$51
Space rental			
150 square feet	$36,000	$2,304	$576
Subtotal	$77,900	$4,986	$1,246
Overhead (50% of total)	$38,950	$2,493	$623
Total	$116,850	$7,478	$1,870

*Estimated cost of exercise training program. The breakdown of exercise training includes trainer's salary, cost of equipment, and space rental. Given the 14-month training period and assuming a group of 4 patients, cost of exercise training was estimated at $1,870/patient.

sion to be $7,198, consisting of the cost of hospitalization ($6,689) and the cost of physician visits ($509). The Medical Producers' Price Index figures from the U.S. Bureau of Labor Statistics indicate that during the period between December of 1993 and November of 1999, the cost of hospitalization increased a net 12%, and the cost of physician visits increased a net 14.0%. Therefore, the cost per admission is estimated to be $8,092 in 1999 dollars.

Sensitivity analysis: A sensitivity analysis was conducted to examine the effects of altering the different assumptions in our cost-effectiveness analysis. We varied the following factors: the survival probabilities during the study period of the randomized trial, the rate of the improvement provided by angiotensin-converting enzyme inhibitors, and the reduction in the rate of hospitalization.

RESULTS

Incremental cost of exercise program: In the randomized trial, the hospitalization rate during the follow-up period was 29% in the control group (there were 14 admissions in the control group consisting of 49 patients) and 10% in the exercise group (only 5 of 50 patients in the training group were admitted). Assuming that the hospitalization rates for the training and the control groups were identical after the follow-up period, a reduction of 19%, simply the difference between the 2 groups in hospitalization rate, was obtained for the training group overall. With a 3% discount rate, the resulting saving for the reduction in hospitalization was $1,336/patient. We subtracted this saving from the total cost of the exercise program ($5,282/patient) to express in a consistent manner, the incremental cost of the health intervention program. Hence the additional discounted cost of the exercise program per patient was determined to be $3,227 (Table 3).

Incremental life expectancy: The survival model extended the 1,639-day survival data (14-month ET period plus 1,214 days of follow-up) by an additional 10 years (Figure 1). Survival at the 1,639th day was 82% in the exercise group and 59% in the control group ($p < 0.05$), and 42% and 30%, respectively, after 10 years. The increase in life expectancy attributable to ET was thus represented by the difference between the areas under the 2 curves. The projected life expectancy was 10.24 years for patients in the exercise group and 7.96 years for the control group, resulting in an undiscounted incremental life expectancy of 2.28 years/patient. The 3% discounted incremental life expectancy was 1.82 years/patient (i.e., 182 additional life-years saved per 100 patients in ET).

Cost-effectiveness analysis: An incremental analysis was conducted to assess the cost-effectiveness of the ET program. The cost-effectiveness ratio is expressed as the additional cost of ET over the incremental life-years saved. Discounting was applied to costs and consequences of the exercise program. Assuming that cost will occur in 1 year, the cost of the exercise program was not discounted. Because the reduction in hospitalization rate was observed over a period of 1,639 days, the averted hospitalization cost was discounted for 4 years (a conservative estimate). With a discount rate of 3%, the numerator of the cost-effectiveness ratio consisted of the incremental cost of the exercise program ($3,227/patient), and the denominator consisted of the incremental life-years saved (1.82 years/patient). Doing the simple computation of cost over effect, we obtained the cost-effectiveness ratio of $1,773/life-year saved (Table 3).

Determining the cohort of heart failure patients: To extrapolate the benefits of ET to all US class II and III heart failure patients between ages 55 and 64, we estimated the size of this cohort in the following manner: We took the total US population in 1997 to be 267,636,000 and the proportion in the 55- to 64-year age group to be 8.2% (U.S. Census Bureau of Statistics, September 16, 1998). The prevalence of chronic heart failure in this age group is 9.6%.[18] We estimated that 80% of the patients would be either in class II or III (personal communication Richard Greene, MD, PhD). To compute the size of the cohort population, we multiplied this percentage of class II/III heart failure patients by the size of US population, the proportion of people in the 55- to 64-year age group, and the prevalence of heart failure in this age group. Thus, we estimated that 1.69 million class II/III heart failure persons could benefit from ET.

Sensitivity analysis: SURVIVAL DURING TRAINING PERIOD AND FOLLOW-UP: Because the hazard of death was assumed to be identical for the training and control groups after the first 1,639 days, survival during the training and follow-up periods was the major determinant of the overall increase in survival resulting from ET. The 95% confidence interval of the increase in survival among patients undergoing ET was 5% to

TABLE 3 Cost-Effectiveness of Exercise Program (at a discount rate of 3%)*								
	Cost of Exercise Program Per Patient	Wage Lost from Exercise Program Per Patient	Hospitalization Rate†	Averaged Cost of Hospitalization Per Patient‡	Total Cost§	Incremental Cost of Exercise Program‖	Incremental Life Expectancy (yrs)¶	Cost-Effectiveness Ratio ($ per life-year saved)**
Training group	$2,054	$2,509	10%	$719	$5,282	$3,227	1.82	$1,773
Control group	$0	$0	29%	$2,055	$2,055	—	—	—

*Cost-effectiveness ratio of exercise training in patients with heart failure, expressed as dollars per year of life saved. With a discount rate of 3%, the numerator of the cost-effectiveness ratio, consisting of the incremental cost of exercise program, was estimated at $3,227/patient, and the denominator, expressed as the incremental life-years saved, was determined at 1.82 years/patient. The cost-effectiveness ratio was estimated at $1,773/life-year saved.

† Estimate = number of admissions/number of patients in the group.

‡ Estimate = discounted cost per hospitalization × hospitalization rate.

§ Estimate = cost of exercise program + wage lost per patient + averaged cost of hospitalization per patient.

‖ Estimate = total cost of exercise group − total cost of control group.

¶ Estimate = discounted increment in life expectancy of the training group.

** Estimate = Incremental cost of exercise program/incremental life expectancy of training group.

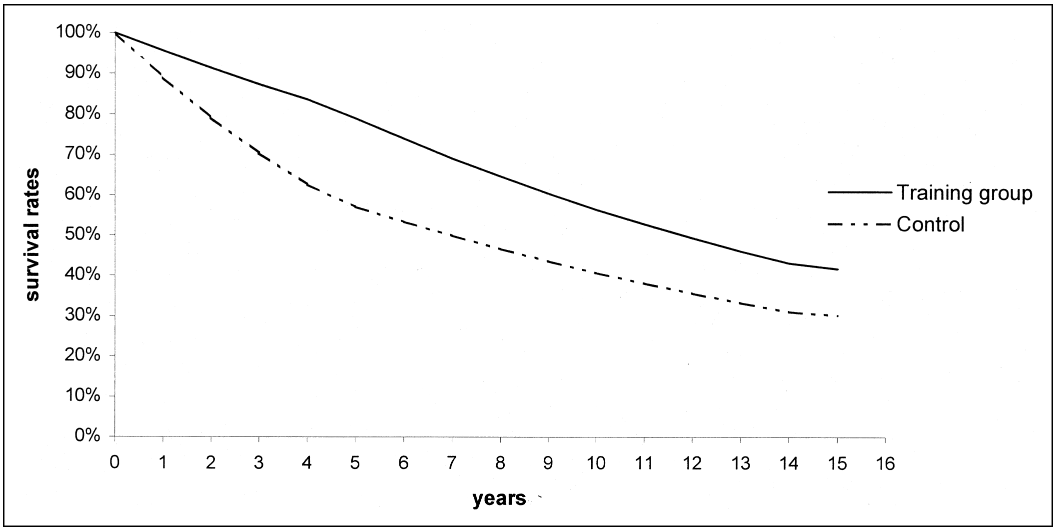

FIGURE 1. Survival curves and life expectancy of the training and control groups. The increase in life expectancy attributable to exercise training was thus represented by the difference between the areas under the 2 curves. The projected life expectancy was 10.24 years for patients in the exercise group and 7.96 years for the control group, resulting in an undiscounted incremental life expectancy of 2.28 years/patient.

40% for the first 1,639 days, resulting in the lower and upper values of life-years saved of 0.39 and 3.19/patient at 3% of the discount rate. The corresponding upper and lower limits of cost-effectiveness were $8,274 and $1,012/year of life saved.

SURVIVAL AFTER FOLLOW-UP: Because >90% of the study subjects in the randomized trial received angiotensin-converting enzymes, we adjusted the estimated survival obtained from National Health and Nutrition Examination-I Epidemiologic Follow-up Survey[13] by 23%, the average improvement in survival for patients on angiotensin-converting enzyme inhibitors.[16] The 95% percent confidence interval of this estimated reduction in mortality is 33% to 12%,[16] and the resulting values of life-years saved are 1.90 and 1.74, respectively, producing a range of cost-effectiveness ratios from $1,698 to $1,855/year of life saved at a discount rate of 3%.

Hospitalization rate: The realized reduction in hospitalization rate in the randomized trial was 19%. The 95% confidence interval of this reduction was 3% to 34%. With a discount rate of 3%, the additional cost of the exercise program would range from $4,317 to $2,178/patient, and the cost-effectiveness ratio would range from $2,372 to $1,197, respectively.

DISCUSSION

Because the present findings have no precedence in the current literature, no direct comparison could be established with other cost-effectiveness values. However, reference can be made to a familiar categorization scheme[19] in which a cost-effectiveness value of ≤$20,000 indicates a highly cost-effective intervention, a value of $20,000 to $40,000 describes consistency with currently funded interventions, and a value >$40,000 indicates marginal or poor cost-effectiveness. On this basis, therefore, ET at a cost of $1,773/year of life saved is designated as a "very attractive" intervention.[20,21]

There are several limitations in terms of the generalization of our findings. We have excluded class IV patients from our cohort under the assumption that class IV patients are not appropriate candidates for ET because they are unable to carry on any physical activity without discomfort. We have assumed in the calculation of our cohort that most class II and III patients are in stable condition of chronic heart failure. Furthermore, because the survival rates were weighted by sex ratio in the study population of the original randomized clinical trial,[1] our results are applicable to a predominantly male population. Previous studies have shown that women with chronic heart failure have better health outcomes than men.[22–25] Also, because the study population in the original randomized trial was between the ages of 55 and 64 years, we could not extrapolate our results to patients in other age groups. However, we have no reason to believe that other age groups will not benefit from ET.

It is likely that our cost-effectiveness ratio was underestimated for the following reasons. First, in the randomized trial,[1] significant improvements in the quality of life (measured using the Minnesota Living with Heart Failure Questionnaire), in the functional capacity such as peak oxygen consumption, and in the thallium activity score were observed in the exercise group compared with the control group.[1] We were unable to include quality-of-life measures in our analysis because the Minnesota Living with Heart Failure Questionnaire is a profile-based quality-of-life instrument,[25] which does not place wellness on a continuum between 0 and 1.0 and has multiple-outcome dimensions. The comparison of different options for the use of common resources requires quantification of health outcomes using a common measurement unit.[26] Consequently, we were unable to compute quality-adjusted life-years. However, the qualitative data indicate that quality adjustment would result in an effectiveness ratio that would more heavily favor ET.

Second, we assumed in our analysis that there was no difference in hospitalization rates between the training and control groups beyond the study period of the randomized trial,[1] and we only took into consideration the difference in hospitalization rates (19%) observed in the follow-up period. If the difference in the rate of hospitalization between the 2 groups continues to diverge after 4 years, the savings in hospitalization could be even more pronounced.

The incremental life expectancy was also computed in a conservative manner. In our survival model, we assumed that the survival curves for the training and the control groups after the exercise period and follow-up will remain equal. However, it is likely that patients in the exercise group would benefit more from ET in the long run and beyond the follow-up period, especially if they adapt the habit of exercising regularly on their own.

Finally, in our calculation of the cost of ET, we used hospital-based costs obtained from major New York City hospitals. These costs are inherently higher than the national average. It is estimated that costs of ET are roughly 20% more expensive in New York City. Thus, the average cost benefit ratio for US patients would be even lower than $1,773/life-year saved.

1. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure. Effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999;99: 1173–1182.

2. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* 1989;79:324–329.

3. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. *Circulation* 1988;78:506–515.

4. Coats AJS, Adamopoulos S, Meyer TE, Conway J, Sleight P Effects of physical training in chronic heart failure. *Lancet* 1990;335:63–66.

5. Coats AJS, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway J, Sleight P. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 1992;85:2119–2131.

6. Belardinelli R, Georgiou D, Scocco V, Barstow TJ, Purcaro A. Low intensity exercise training in patients with chronic heart failure. *J Am Coll Cardiol* 1995;26:975–982.

7. Horning B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic hear failure. *Circulation* 1996;93:210–214.

8. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, Yu J, Adams V, Niebauer J, Schuler G. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998;98:2709–2715.

9. Minotti JR, Johnson EC, Hudson TH, Zuroske G, Murata G, Fukushima E, Cagle, TG, Chick TW, Massie BM, Lcenogle MV. Skeletal muscle response to exercise training in congestive heart failure. *J Clin Invest* 1990;86:751–758.

10. Adamopoulos S, Coats AJS, Brunotte F, Arnolda L, Meyer T, Thompson CH, Dunn JF, Stratton J, Kemp GJ, Radda GK, Rajagopalan B. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol* 1993;21:1101–1106.

11. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programs. 2nd ed. New York: Oxford University Press, 1997.

12. Bigger JT Jr, Parides MK, Rolnitsky LM, Meier P, Levin B, Egan DA. Changes in sample size and length of follow-up to maintain power in The Coronary Artery Bypass Graft (CABG) patch trial. *Controlled Clin Trials* 1998; 19:1–14.

13. Cornoni-Huntley J, Barbano HE, Brody JA. National health, and nutrition examination I—epidemiologic follow-up survey. *Public Health Rep* 1983;96: 245–251.

14. Schocken D, Arrieta M, Leaverton P. Prevalence, and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301–306.

15. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–677.

16. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality, and morbidity in patients with heart failure. *JAMA* 1995;273:1450–1456.

17. Delea T, Vera-Llonch M, Richner R, Fowler M, Oster G. Cost-effectiveness of carvedilol for heart failure. *Am J Cardiol* 1999;83:890–896.

18. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996; 276:1253–1258.

19. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost-effectiveness analysis in heart diseases. *Prog Cardiovasc Dis* 1995;37:243–271.

20. Ades P, Pashkow F, Nestor J. Cost-effectiveness of cardiac rehabilitation after myocardial infarction. *J Cardiopulm Rehabil* 1997;17:222–231.

21. Ades P, Huang D, Weaver S. Cardiac rehabilitation participation predicts lower rehospitalization costs. *Am Heart J* 1992;123:916–921.

22. Petrie M, Dawson N, Murdoch D, Davie A, McMurray J. Failure of women's hearts. *Circulation* 1999;99:2334–2341.

23. Chin M, Goldman L. Gender differences in 1-year survival, and quality of life among patients admitted with CHF. *Med Care* 1998;36:1033–1046.

24. Kimmelstiel C, Goldberg R. Congestive heart failure in women. focus on heart failure due to coronary artery disease and diabetes. *Cardiology* 1990; 77(suppl 2):71–79.

25. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire. *Am Heart J* 1992;124:1017–1024.

26. Staquet MJ, Hays RD, Fayers PM. Quality of Life Assessment in Clinical Trials. New York: Oxford University Press, 1998.