Support for aerobic exercise training in heart failure (HF) patients

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CLINICAL SCENARIO: HF in the community is overwhelmingly a disorder of the elderly (Fleg, 2002) and medical advances are allowing patients with significant HF to live longer. Health professionals recommend exercise as part of a comprehensive treatment plan for HF management. It's important to understand the effects of exercise in a typical HF population.

FOCUSED CLINICAL QUESTION: Does daily progressive symptom-limited walking improve functional status (as measured by six minute distance) in elderly patients with moderate to severe HF?

SUMMARY of Search, 'Best' Evidence' Appraised, and Key Findings:

- 2 RCT's were found: 1 failed to find consistent benefits of endurance exercise in an elderly HF population. 1 found that moderate aerobic exercise training in HF patients was safe, yielded improvement in 6-MWT at 3 months, and produced modest reductions in clinical events.
- 2 systematic reviews found evidence to support the safety and benefits of exercise in patients with HF.
- 1 pilot study found that aerobic, functional and resistance exercise in elderly HF patients is well-tolerated. Though the study was not powered to detect changes in outcome, the results were encouraging.

CLINICAL BOTTOM LINE: The above studies concluded that exercise is safe, well-tolerated and provides neutral to modest improvements in the health status of patients with HF. These findings support moderate intensity aerobic exercise for a typical HF patient.

Limitation of this CAT: This critically appraised paper was prepared for a graduate course assignment and has not been peer-reviewed by one other independent person/an instructor.

SEARCH STRATEGY:

Terms used to guide Search Strategy:

- **P**atient/Client Group: Adults with HF aged 65+.
- **I**ntervention: Walking or Exercise
- **O**utcome(s): Improved function as measured by six minute walk test (6-MWT)

Databases and Sites Searched	Search Terms	Limits Used
PEDro MEDLINE EMBASE CINAHL Cochrane Library Google Scholar	Chronic heart failure OR heart failure OR congestive heart failure AND Aged AND Walk* OR Exercise OR Physical Activity AND functional status OR six minute walk test OR 6-minute walk test Author search	Published: 2000-2010 Aged: 65+ years Publication type: Review RCT Scholarly

INCLUSION and EXCLUSION CRITERIA

- Inclusion
    1. Moderate-Severe HF patients
    2. Aged 65+
    3. 6-MWT as functional outcome
    4. Moderate intensity aerobic exercise, 3-5 days/week (feasible in practice)

- Exclusion
    1. Specific sub-groups of HF

RESULTS OF SEARCH

Table 1: Summary of Study Designs of Articles Retrieved

Study Design/ Methodology of Articles Retrieved	Level*	Number Located	Author (Year)
Multi-center RCT	1b	1	O'Connor et al. (2009)
Single-center RCT	1b	1	Brubaker et al. (2009)
Systematic Review of RCTs	1a	1	Chien-Lin et al. (2008)
Systematic Review of RCTs	1a	1	Tai et al. (2008)
Pilot study (case series, convenience sample)	4	1	Witham et al. (2008)

- No study matched P/I/O exactly
- The multi-center RCT included P but did not specifically focus on the elderly, met the I criteria and used O as a secondary outcome.
- The single-center RCT met P/I criteria, used O as a secondary outcome, but was conducted 1995-1999.
- Both systematic reviews had small numbers of elderly patients and compared different exercise protocols using various outcomes. The most appropriate study from each was performed in 2005 (thus not one of the five most recent) and it met P/O criteria but not I.
- The pilot study met P/O but not I.

BEST EVIDENCE

O'Connor et al. (2009). Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure HF-Action Randomized Controlled Trial was identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting this study were:

- No upper age limit. Encouragement from study leadership to strive for higher recruitment of elderly (Kitzman, 2010).
- Sub-group analysis relevant to my question, i.e.: >70 years old; LVEF <25%; NYHA class III or IV.
- 6-MWT as a secondary outcome.
- Strong design

SUMMARY OF BEST EVIDENCE

Table 2: Description and appraisal of **O'Connor et al. (2009). Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure HF-Action Randomized Controlled Trial.**

Aim/Objective of the Study: To test the efficacy and safety of aerobic exercise training among patients with NYHA classes II to IV HF receiving evidence-based care.

Study Design: Randomized controlled clinical trial. Patients were randomized 1:1 using a permuted block randomization scheme, stratified by clinical center, from April 2003 through February 2007. Patients and investigators were not blinded. The primary end-point was all-cause mortality or hospitalization. Median follow-up was 30 months. Cardiopulmonary exercise testing (CPX) was performed at time of randomization, at 3, 12 and 24 months. 6-MWT was performed at 3 and 12 months. Patients completed a physical activity questionnaire at baseline, 6, 12, 24 months, 3 years and final visit.

Setting: Clinical settings ranged from academic tertiary care centers to rural private practices within Canada, U.S. and France (82 centers total).

Participants: 2331 medically stable out-patients with HF. Enrollment criteria included NYHA class II-IV despite at least six weeks of optimal therapy, left ventricular ejection fraction (LVEF) <35% and ability/willingness to undergo exercise training. 28% were women, 40% minorities, 18% >70 years, 37% had NYHA class III or IV symptoms, and 95% were on guideline-based medical therapy. Mean EF was 25%. Exclusion criteria included: comorbidities/limitations that could interfere with exercise, age <18 years, recent or planned cardiovascular event or procedure, performance of regular exercise, use of devices that limit the ability to achieve target heart rates, exercise testing results that preclude safe exercise training, HF secondary to primary valvular disease or congenital heart disease.
1172 patients were randomized to usual care (17 lost to follow-up, 46 withdrew consent), and 1159 to exercise group (22 lost to follow-up, 37 withdrew consent). Searches of death databases were conducted to assess if lost patients had died.

Intervention Investigated: The researchers made efforts to ensure all patients were receiving appropriate guideline-based care before entering the trial (drugs, device-therapies). All patients received an education booklet on HF management including recommendation of 30 minutes (as tolerated) of moderate activity on most days, as recommended by the

American College of Cardiology/American Heart Association. Personnel did not provide a formal exercise program to the usual care group.
The exercise group first participated in supervised training 3 times/week. Patients began exercising at low intensity and then progressed to moderate intensity when able. Moderate intensity is defined as activity that does not cause sweat or breathlessness. This group-based program included walking, treadmill or stationary cycling, initially for 15-30 minutes at 60% of heart rate reserve (HRR), then increasing to 30-35 minutes at 70% of HRR after 6 sessions. After 18 supervised sessions, patients began home-based exercise and fully transitioned to 40 minutes of aerobic exercise 5 times/week at home after 36 sessions. Patients in the exercise group were provided home cycle/treadmill and heart rate monitors.

Outcome Measures: Primary end-point was combined *all-cause* mortality and *all-cause* hospitalization. Secondary outcomes were *cardiovascular* mortality or *cardiovascular* hospitalization, peak VO2, 6-MWT distance, and NYHA functional class. RPE and Polar heart rate monitors were used to verify exercise intensity. Log sheets and the Physical Activity Questionnaire were used to quantify activity over a 7 day period. Additional outcome measures were used for ancillary HF-ACTION studies.
Follow-up clinic visits occurred in both groups every 3 months for the first 24 months and yearly thereafter. Study coordinators made follow-up telephone calls once every 2 weeks for the first 9 months, then monthly until month 24, then every 3 months thereafter. Statistical comparisons were performed according to the intention-to-treat principle therefore all patients from both groups were included in primary analysis regardless of crossover or nonadherence. Follow-up was to a four year maximum.

Main Findings: All statistical tests were 2-tailed. Relative risks were derived from the Cox proportional hazards model and expressed as hazard ratios with 95% confidence intervals.
<u>Primary end-point:</u>
759 patients (65%) in the exercise group and 796 patients (68%) experienced death or hospitalization from *all*-cause. In primary analysis (log rank test used to adjust for ischemic vs. non-ischemic HF), exercise training resulted in a nonsignificant reduction in primary end-point (HR 0.93[95% CI, 0.84-1.02]; p=.13). The absolute reduction in primary event rate was 4% at 3 years. Four baseline characteristics (duration of CPX, LVEF, Back Depression Inventory II score, and history of Afib/Aflutter) were highly prognostic of primary end-point, and after adjusting for these, the exercise group had a statistically significant 11% (HR 0.89[95% CI, 0.81-0.99]; p=.03) reduction in primary end-point. There was no significant difference in the incidence of death between groups (16% in exercise, 17% in usual care); HR 0.96[95% CI, 0.79-1.17]; p=.70). At least one hospitalization occurred in 63% of patients in

exercise group and 65% in usual care group. 37 patients in the exercise group had at least one hospitalization within 3 hours of exercise, 22 patients in the usual care group had such a hospitalization. Subgroup analysis of primary end-point was performed for many covariates including age >70, baseline NYHA class, LVEF, and showed no significant interaction of exercise with any of these subgroups.

Secondary end-point:

The researchers also looked at combined *cardiovascular* mortality and *cardiovascular* hospitalization and found a nonsignificant reduction in the exercise vs. usual care group (HR 0.92[95% CI, 0.82-1.03]; p=.14) as well as after adjustment for prognostic factors (HR 0.91[95% CI, 0.82-1.01]; p=.09). They also found a nonsignificant reduction in *cardiovascular* mortality or *heart failure* hospitalization in the exercise group vs. usual care group (HR 0.87,[95% CI, 0.75-1.00]; p=.06), however after adjustment for prognostic factors, exercise produced a statistically significant reduction of 13% in this end-point (HR 0.85[95% CI, 0.74-0.99]; p=.03).

CPX:

At 3 months follow-up, the exercise group had a greater improvement in cardiopulmonary exercise test time (1.5 vs. 0.3 minutes, p<.001) and in peak VO2 (0.6 vs 0.2 mL/min/kg, p<.001). At 12 months, the difference in CPX time and peak VO2 remained.

6-MWT: At 3 months, 166 (19%) in usual care group had an improvement >50m in 6-MWT compared to 273 (28%) in the exercise group. At 12 months, there was no significant difference between groups.

Table 1: Change in 6-MWT in m:

	Usual Care	Exercise Group	P value
Baseline to 3-months (n= 1835)	5(-28 to 37)	20(-15 to 57)	< .001
Baseline to 12- months (n= 1444)	12(-30 to 55)	13(-28 to 61)	.26

Original Authors' Conclusions: The HF-ACTION trail was the largest RCT of exercise training ever performed. Exercise training was safe but provided non-significant reduction in mortality or hospitalization in patients with HF with NYHA class II to IV symptoms on guideline-based medical therapy.

After adjusting for highly prognostic characteristics, exercise did significantly reduce the risk for *all-cause* mortality or *all-cause* hospitalization, as well as *cardiovascular* mortality or *heart failure* hospitalization.

There was a significant difference in CPX time and peak VO2 at 3- and 12-months. There was significant difference in 6-MWT distance at 3-months, but not at 12-months. The study supports a prescribed exercise program in this population.

Critical Appraisal:

Validity: A literature review described the prevalence of HF and the lack of definitive clinical outcome data pertaining to exercise in this population. Recruitment strategy was not well documented. Randomization was described and a table showed that groups were similar in important characteristics. Bias might have occurred in selecting "willing" participants who might be more motivated.
Patients and investigators were not blinded due to the nature of the intervention, which could result in favourable attention to the exercise group. The primary outcomes were adjudicated by a committee blinded to group assignment.
Patients were evaluated at appropriate intervals using appropriate measures. 6-MWT has been shown to be reproducible, reliable, and valid in HF patients (Guyatt et al., 1985; Pollentier et al., 2010). CPX were performed at different facilities by different technicians (hence variability) and patients who returned for 12-month CPX and 6-MWT may have had better health status than those who did not (n= 1444 for 6-MWT, n= 1476 for CPX).
The intervention was well described and adjustments were made for beta-blocker use and angina. The study personnel were not well-described and site variation was a source of bias.
To reduce attention bias, both groups received the same number of interactions except in cases of poor compliance (when additional calls were permitted which could favour the exercise group). Telephone conversations were scripted to maintain consistency.
Recall bias might have been a factor in activity logs (also, patients wanting to "please" the researchers may have overstated the exercise performed). Missing data on home exercise is also a limitation.
Extensive measures were taken to promote adherence in exercise group (provision of equipment, frequent follow-up, logistical assistance, logs).
The exercise group wasn't permitted to cross-train. 55% of patients in the control group were dissatisfied with their assignment and could have exercised or self-referred (crossover), favouring the control group.
The design was based on a traditional 36-session cardiac rehab model followed by home exercise (Whellan et al., 2007) thus is easily translatable to clinical practice.
The author of this CAT grades the Quality Score (taken from Law & MacDermid, 2008, Appendix M and N) as 45/48.

Interpretation of Results
The broad population and variability in practice settings increases generalizability. However, only 18% of patients were >70 years. Older patients were perhaps excluded due to inability to perform CPX, increased incidence of valvular disease, or unwillingness to participate.

Researchers controlled for many variables, thereby decreasing variability and making it easier to detect differences that might not have otherwise existed.
The original target enrolment was 3000 patients to provide 90% power to detect an 11% reduction in the 2-year primary event rate under several assumptions based from previous studies. The planned median follow-up was 2.5 years. Interim calculations based on higher overall event rate in the control group revealed that a sample size of 2300 was required for 90% statistical power, so target sample size was reduced.
Suboptimal adherence in the exercise group and crossover might have resulted in diminished exercise benefits.
The authors explain that change from a nonsignificant to a significant result after adjusting for prognostic factors can occur if treatment differences are close to significance. Reduction in end-point of 11 and 13% (after adjustment) is clinically meaningful, especially given that patients were on optimal medical therapy.
The primary end-point of all-cause mortality or hospitalization was chosen to capture the full clinical effect of exercise training (Whellan et al., 2007)
Loss to follow-up was minimal (1.7%) for the primary outcome.

Summary/Conclusion: The HF-ACTION results support progressive symptom-limited walking as exercise training in patients with moderate to severe HF. Exercise provided a significant short-term improvement in 6-MWT distance at 3 months but did not carry over to 12 months. Subgroup analysis seemed to show that there were no significant differences in exercise effects in >70 year old versus <70 year olds, but the study did not look specifically at the effects of exercise in elderly HF patients. Study results should thus be interpreted in the context of a younger than typical HF population.
Neutral to modest results can be explained by:

- Insufficient training effect due to blunting effects of beta-blockers
- Crossover
- Sub-optimal exercise adherence due to chronic symptoms, comorbidities, diminishing motivation over time.
- Missing data

IMPLICATIONS FOR PRACTICE, EDUCATION and FUTURE RESEARCH

Health professionals should recommend exercise for HF patients. Future research should evaluate the best type of exercise, and effects in the elderly.
The 6-MWT is a functional, economical physiotherapy tool shown to significantly predict peak VO2 (Pollentier et al., 2010) and is perhaps more appropriate than CPX for elderly patients with comorbidities. A change of 25m in 6-MWT distance is considered clinically relevant (Guyatt

et al., 1985). Flynn et al. (2009) found that a 49.7m change on the 6-MWT corresponded to a meaningful improvement in quality of life. Logistics such as transportation and caring for a dependent spouse should be addressed to increase participation of elderly in studies (Fleg, 2002). Different outcomes such as ability to return to community and function should also be assessed in the elderly (Kitzman, 2010).
This article was one of nine derived from the HF-ACTION study.

References

Brubaker, P. H., Moore, J. B., Stewart, K. P., Wesley, D. J., & Kitzman, D. W. (2009). Endurance exercise training in older patients with heart failure: Results from a randomized, controlled, single-blind trial. *Journal of the American Geriatrics Society, 57*(11), 1982-1989.

Chien, C., Lee, C., Wu, Y., Chen, T., & Wu, Y. (2008). Home-based exercise increases exercise capacity but not quality of life in people with chronic heart failure: A systematic review. *The Australian Journal of Physiotherapy, 54*(2), 87-93.

Fleg, J. L. (2002). Can exercise conditioning be effective in older heart failure patients? *Heart Failure Reviews, 7*(1), 99-103.

Flynn, K. E., Piña, I., Whellan, D. J., Lin, L., Blumenthal, J. A., Ellis, S. J., Fine, L. J., Howlett, J. G., Keteyian, S. J., Kitzman, D. W., Kraus, W. E., Miller, N. H., Schulman, K. A., Spertus, J. A., O'Connor, C., & Weinfurt, K. P. (2009). Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA: Journal of the American Medical Association, 301*(14), 1451-1459.

Guyatt, G. H., Sullivan, M. J., Thompson, P. J., Fallen, E. L., Pugsley, S. O., Taylor, D. W., & Berman, L. B. (1985). The 6-minute walk: A new measure of exercise capacity in patients with chronic heart failure. *Canadian Medical Association Journal, 132*(8), 919-923.

Kitzman, D. W., & Rich, M. W. (2010). Age disparities in heart failure research. *JAMA: The Journal of the American Medical Association, 304*(17), 1950-1951.

Law, M. C., & MacDermid, J. (2008). *Evidence-based rehabilitation : A guide to practice* (2nd ed.). Thorofare, NJ: Slack.

O'Connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., Leifer, E. S., Kraus, W. E., Kitzman, D. W., Blumenthal, J. A., Rendall, D. S., Miller, N. H., Fleg, J. L., Schulman, K. A., McKelvie, R. S., Zannad, F., Pina, I. L., & HF-ACTION, I. (2009). *JAMA, 301*(14), 1439-1450. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=medl&AN=19351941

Pollentier, B., Irons, S. L., Benedetto, C. M., DiBenedetto, A., Loton, D., Seyler, R. D., Tych, M., & Newton, R. A. (2010). Examination of the six minute walk test to determine functional

capacity in people with chronic heart failure: A systematic review. *Cardiopulmonary Physical Therapy Journal, 21*(1), 13-21.

Tai, M., Meininger, J. C., & Frazier, L. Q. (2008). A systematic review of exercise interventions in patients with heart failure. *Biological Research for Nursing, 10*(2), 156-182.

Whellan, D. J., O'Connor, C.,M., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., Leifer, E. S., Kraus, W. E., Kitzman, D. W., Blumenthal, J. A., Rendall, D. S., Houston-Miller, N., Fleg, J. L., Schulman, K. A., & Piña, I.,L. (2007). Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): Design and rationale. *American Heart Journal, 153*(2), 201-211.

Witham, M. D., Argo, I. S., Johnston, D. W., Struthers, A. D., & McMurdo, M. E. T. (2007). Long-term follow-up of very old heart failure patients enrolled in a trial of exercise training. *The American Journal of Geriatric Cardiology, 16*(4), 243-248.