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# **Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis**

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## **Abstract**

**Aim** - To determine the effect of exercise training on clinical events and health-related quality of life (HRQoL) of patients with systolic heart failure.

**Methods & Results** - We searched electronic databases including Medline, EMBASE and Cochrane Library up to January 2008 to identify randomised controlled trials (RCTs) comparing exercise training and usual care with a minimum follow up of 6-months. Nineteen RCTs were included with a total of 3,647 patients, the majority of whom were male, low to medium risk, New York Heart Association class II to III with a left ventricular ejection fraction of < 40%. There was no significant difference between exercise and control in short-term ( $\leq 12$  months) or longer term all cause mortality or overall hospital admissions. Heart failure related hospitalisations were lower (relative risk: 0.72, 95% CI: 0.52 to 0.99) and HRQoL improved (Standardised mean difference: -0.63, 95% CI: -0.80 to -0.37) with exercise therapy. Any effect of cardiac exercise training on total mortality and HRQoL was independent of degree of left ventricular dysfunction, type of cardiac rehabilitation, dose of exercise intervention, length of follow-up, trial quality, and trial publication date.

**Conclusion** - Compared to usual care, in selected heart failure patients, exercise training reduces heart failure-related hospitalisations and results in clinically important improvements in HRQoL. High quality RCT and cost effectiveness evidence is needed of the effect of exercise training in community based settings and in more severe heart failure patients, elderly people and women.

## Introduction

Patients with chronic heart failure (CHF) experience marked reductions in their exercise capacity which has detrimental effects on their activities of daily living, health-related quality of life (HRQoL) and ultimately their hospital admission rate and mortality.<sup>1</sup>

Exercise training is often a component of rehabilitation programmes offered to patients with CHF.<sup>1</sup> In 2004, a Cochrane systematic review by Rees et al on the effect of exercise-based interventions on people with heart failure demonstrated a clear improvement in short-term exercise capacity.<sup>2</sup> Twenty nine trials were included in that review, only one of which reported longer-term hospitalisations and mortality. The remaining trials were largely small scale and did not aim to assess clinical events. The ExTraMATCH Collaborative Group published, also in 2004, an individual patient data meta-analysis.<sup>3</sup> This review reported a reduction in the mortality of CHF patients who received exercise based intervention (hazard ratio 0.65, 95% CI 0.46 to 0.92). However, the ExTraMATCH study was based on a limited bibliographic literature search (Medline plus hand-searching of selected leading cardiac journals) and included unpublished data. It has therefore been difficult to verify the data and comprehensiveness of this meta-analysis; several of the trials included in the Cochrane review were not included in the ExTraMATCH review. Reanalysis of the ExTraMATCH trial data using meta-analytic methods has shown that the effect of exercise-training was not statistically significant when compared to control (relative risk 0.88, 95% CI: 0.70 to 1.10).<sup>4</sup> Van Tol and colleagues, in 2006, published a meta-analysis supporting the improvements in exercise capacity as seen in the previous Cochrane review.<sup>5</sup> They also saw an improvement in quality of life as measured by the Minnesota Living with Heart Failure (MLWHF) Questionnaire. In 2007, Hawkowsky et al published a systematic review demonstrating the positive effect of exercise based intervention on cardiac remodeling in patients with CHF.<sup>6</sup> In summary, to date, there is consensus on the positive effect of exercise on exercise capacity but the effects on hospital admission rates, mortality and HRQoL remains uncertain.

The aim of the present study was to determine the impact of exercise based interventions on the mortality, hospitalisation rate, HRQoL and cost effectiveness of patients with systolic CHF.

## Methods

The review was undertaken in accord with the methods of The Cochrane Collaboration.<sup>7</sup>

### Study Selection

Previous meta-analyses and systematic reviews were searched for studies.<sup>2-5,8-10</sup> The following electronic databases were searched from searching end date of the previous Cochrane systematic review (2001) and up to January 2008: Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, EMBASE, MEDLINE, CINAHL, PsycINFO, the NHS Centre for Reviews and Dissemination (CRD) databases (Health Technology Assessment (HTA) and Databases of Abstracts of Reviews of Effects (DARE)). Conference proceedings were searched on Web of Science: ISI Proceedings. Using search filters were limited to randomised controlled trials (RCTs), systematic reviews, and meta-analyses and humans. The search was designed as part of broader review that included the update of number of cardiac rehabilitation reviews (see Appendix 1). No language or other limitations were imposed. Two reviewers independently scanned all the titles and abstracts and identified potentially relevant articles to be retrieved. Where there was uncertainty, full-text copies of papers were obtained.

### Inclusion and exclusion criteria

Studies were considered eligible if they were RCTs; included CHF patients (> 18 years) with either ischaemic or non-ischaemic aetiology and specified criteria for the diagnosis of systolic heart failure such as an objective assessment of left ventricular ejection fraction or by clinical findings; received an exercise based intervention either alone or as part of a comprehensive cardiac rehabilitation program (defined as programs also including such components as health education and psychological treatment); compared to standard medical care or attention placebo control group, and with a minimum follow up of six months. Four categories of outcome were sought: mortality (all cause, death due to heart failure and sudden cardiac death); hospital admission/re-admission rates and HRQoL assessed by a validated outcome measure (e.g. Minnesota Living with Heart Failure [MLWHF] Questionnaire or Short-Form 36 [SF-36]); and cost effectiveness. Trials recruiting patients with heart failure associated with normal systolic function were excluded as were studies that included patients who had previously been offered cardiac rehabilitation. Full-text papers of all potentially eligible trials were independently assessed by two reviewers and disagreements were resolved by discussion.

### **Data extraction and risk of bias assessment**

The following information categories were extracted: details of the study population and their baseline characteristics; details of the intervention (exercise training prescription and co-interventions) and control; length of follow-up; and details of individual outcome results. In order to assess of risk of bias, the following factors were considered: appropriate method of randomisation (e.g., statement of computer-generated numbers) sequence, and an adequate concealment of randomisation (e.g., randomisation codes been kept from those involved in running the trial), whether there was blinding (particularly blinding of outcome given the difficulties of blinding patients and carers given the nature of the intervention), whether all outcomes and losses to follow up/drop-outs were reported and whether intention to treat analysis was performed.<sup>7</sup> Study authors were contacted to seek clarification on issues of reporting or to provide further outcome detail. Data extraction and risk of bias assessment was undertaken by a single reviewer using a standardised form and verified by a second reviewer.

### **Statistical analysis**

Dichotomous outcomes were expressed as relative risks (RR) and 95% confidence intervals (CI) were calculated. Net changes in continuous variables were compared (i.e. exercise based intervention minus control group differences) and a weighted mean difference (WMD) or standardised mean difference (SMD) together with 95% CI expressed for each study.<sup>7</sup> Heterogeneity amongst included studies was explored qualitatively (with comparison of the characteristic of included studies) and quantitatively (using the chi-squared test of heterogeneity and  $I^2$  statistic). A fixed-effects meta-analysis was used except when statistical heterogeneity was identified when the more conservative random-effects model was used.<sup>11</sup> In studies reporting more than one HRQoL outcome, to prevent double counting in meta-analysis, we chose one of the reported HRQoL outcomes at random. The inference of meta-analysis did not change when selecting the alternative HRQoL measure score. Sensitivity analysis was undertaken to examine the effect of omission of HF-ACTION trial.<sup>xxii</sup> Meta-regression was used to examine the influence of a number of factors on all cause mortality and HRQoL. The study level factors included: mean left ventricular ejection fraction; dose of exercise intervention ('dose' was calculated as the number of weeks multiplied by the number of sessions per week, multiplied by the duration of the session in hours); type of exercise (aerobic training alone or aerobic plus resistance training); type of cardiac

rehabilitation (exercise-based cardiac rehabilitation vs. comprehensive cardiac rehabilitation); mean age; gender (% male); setting (hospital only, both hospital and home or home only); and duration of follow-up. In order to assess the potential effect of a change in the standard of usual care over time we added year of publication as an additional study level factor (pre- vs. post 2000) to reflect when beta-blockers, angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors became established therapies for CHF.<sup>12</sup> Funnel plots (i.e. scatter plots of the mean intervention effect versus the inverse of variance of the intervention effect for each study) were used to explore the possibility of publication bias.<sup>13</sup> All analyses were performed using RevMan, version 5.0 and STATA version 10.0.

## Results

### Identification and selection of studies

Our bibliographic search yielded 11,561 titles. After a review of the titles and abstracts of these, 65 full papers were retrieved and assessed. In total 50 papers were excluded: 19 with follow up less than 6 months, 21 with outcomes not relevant to this review (e.g. exercise capacity), three with an inappropriate study population and six were reviews and one was a study protocol. Therefore the total number of included trials was 19 (23 papers) (See Figure 1). One trial was split into two sub-studies to reflect that the included patients were randomised to two different exercise interventions, both compared to usual care.<sup>xv</sup> The protocol of the HF-ACTION trial<sup>xxii</sup> was identified by our search and so the trial was included, despite it being published after January 2008.

### Description of randomised controlled trials

The 19 trials contained a total of 3,647 patients, some 60% of which were contributed by the HF-ACTION trial<sup>v, xiv</sup> (N=2,331) (see Table 1). Recruited subjects were mainly uncomplicated CHF patients with NHYA class II and III and a left ventricular ejection fraction of less than 40%. Mean age ranged from 43 to 72 years and the majority was male (43 to 100%). With one exception, all trials were judged to be exercise-only interventions. In addition to exercise training, Austin et al provided patients with education and psychological interventions (i.e. comprehensive cardiac rehabilitation).<sup>i,ii</sup> All studies used the modality of aerobic training with five also using resistance training. Exercise training programmes ranged widely across the studies: duration - 15 to 120 minutes per session, frequency - 2 to 7 sessions/week, intensity - 40% maximum heart rate to 85% of maximum oxygen uptake (VO<sub>2</sub>max), overall duration - 24 weeks to 3-years. Exercise was centre delivered in 12 studies, entirely home based in one study and initially within centre and then at home in the remainder. Both intervention and control patients received usual care including medication and education advice, although controls received no formal exercise training. Four trials reported a follow up longer than 12 months.<sup>ii,iii,xviii,xix</sup>

### Risk of bias

A number of studies failed to give sufficient detail to assess their potential risk of bias (Table 2). Details of generation and concealment of random allocation sequence and intention to treat analysis were particularly poorly reported. Only the studies of Austin et al<sup>i</sup>, Hambrecht et al,<sup>xii</sup> McKelvie et al<sup>xvii</sup> and the HF-ACTION trial<sup>xxii</sup> provided an adequate description of the



randomisation process. Nevertheless, in none of the studies was there objective evidence of imbalance in baseline characteristics. Four trials stated that they performed intention to treat analysis.<sup>i, vi, xiii, xix</sup> However, although often not stated, many studies appeared to compare exercise and control group outcomes according to initial random allocation. Where reported, losses to follow up varied considerably across studies and the impact of losses to follow up or drop out was only examined in a few trials. Only the studies of Koukovou et al,<sup>xvi</sup> McKelvie et al,<sup>xvii</sup> and Willenheimer et al<sup>xxiii</sup> reported blinding of outcome assessment.

## **Outcomes**

Pooled outcome findings are summarised in Table 3.

### *Mortality*

There was no difference in pooled all-cause mortality between the exercise based intervention and control groups up to 12-months follow up (RR: 1.02, 95% CI: 0.70 to 1.51, heterogeneity chi-squared = 3.89, p = 0.952, Figure 2) or when pooling the four trials with follow up of longer than 12-months (RR 0.91, 95% CI: 0.78 to 1.06, heterogeneity chi-squared = 5.06, p = 0.167, e-Figure 1). A significant reduction in longer term mortality was seen with exclusion of HF-ACTION trial (RR: 0.62, 95% CI: 0.39 to 0.98). There is a lack of consistency in reporting deaths due to heart failure or sudden cardiac death.

### *Hospital Admissions*

Whilst there was weak evidence of a trend towards a reduction in the overall hospital admission rate up to 12-months (RR 0.79, 95% CI: 0.58 to 1.07, heterogeneity chi-squared = 5.07, p = 0.535, e-Figure 2) there was no evidence of an effect beyond 12 months (RR 0.96, 95% CI: 0.90 to 1.02, heterogeneity chi-squared = 4.74, p = 0.192, e-Figure 3). This longer term result was consistent with the exclusion of HF-ACTION (RR: 0.75, 95% CI: 0.52 to 1.08). There was a significant reduction in heart failure specific hospital admissions with exercise-based interventions (RR: 0.72, 95% CI: 0.52 to 0.99, heterogeneity chi-squared = 7.17, p = 0.305, e-Figure 3).

### *HRQoL*

Ten studies assessed HRQoL using a validated scale. Most used the disease specific Minnesota Living with Heart Failure (MLWHF) scale, others included scales were EuroQoL (EQ-5D), Psychological Wellbeing Index (PGWB), Patients Global Assessment of Quality of Life (PGAQoL), Spritzer's Quality of Life Index (QLI) and the recently developed Kansas City Cardiomyopathy Questionnaire (KCCQ). The study by Gottlieb only reported HRQoL values at follow up in the exercise group but not the controls (see e-Table 1).<sup>ix</sup> Across the five

studies that reported total MLWHF score, there was strong evidence of improvement with exercise (mean difference: -10.3, 95% CI: -15.9 to -4.8, heterogeneity chi-squared = 17.49,  $p = 0.004$ , e-Figure 4). Pooling across all studies regardless of the HRQoL measure used, there was also strong evidence of improvement with exercise (standardised mean difference: -0.57, 95% CI: -0.83 to -0.31, heterogeneity chi-squared = 45.03,  $p < 0.0001$ , Figure 4); a finding that remained on exclusion of HF-ACTION (standardised mean difference: -0.63, 95% CI: -0.89 to -0.37).

### *Cost Effectiveness*

Only the Belardinelli trial reported a cost effectiveness analysis.<sup>viii</sup> Fourteen-month survival and healthcare costs were extrapolated to 15.5 years and incremental cost per life year gained ratio for exercise-based intervention versus controls were compared. The estimated incremental cost for the exercise-based intervention group, \$US 3,227/patient, was calculated by subtracting the averted hospitalisation cost, \$US 1,336/patient, from the cost of exercise training and wage lost due to exercise training estimated at \$US 4,563/patient. For patients receiving exercise training, the estimated increase 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 exercise in patients was determined at \$US 1,773/life-year saved, at a 3% discount rate at 1999 costs.

### **Meta-regression**

Univariate meta-regression analyses showed no evidence of a relationship between the effect of exercise training and all-cause mortality and any of the covariates. There was a significantly ( $P=0.04$ ) larger improvement in HRQoL with exercise training in trials in a centre-setting compared to a home-setting. No other covariates were related to the effect of exercise training on HRQoL (see Table 4).

### **Small study bias**

Whereas there was no evidence of funnel plot asymmetry for either all-cause mortality (e-Figure 5) and overall hospitalisations (e-Figure 6), the funnel plot for HRQoL outcomes did demonstrate asymmetry (e-Figure 7). Given the statistically significant small study bias seen with HRQoL, regression based adjustment was applied and it was found that improvement in HRQoL with exercise training remained (standardized mean difference; -0.16, 95% -0.02 to -0.29).<sup>14</sup>



## Discussion

This systematic review shows that in systolic CHF patients, exercise-based intervention reduces the level of hospitalisations due to heart failure and improves HRQoL. We identified trials which consistently reported higher levels of HRQoL. In those using the Minnesota Living with Heart Failure (MLWHF) questionnaire, exercise intervention groups were on average 10 points higher than controls. A difference of 4 points has been shown to represent a clinically important and meaningful difference for the patient.<sup>15</sup> The HRQoL effects of exercise therapy appears to be consistent across a number of CHF groups (i.e. age, gender and left ventricular ejection fraction) as well as range of exercise intervention delivery strategies (exercise dose, aerobic only exercise versus aerobic plus resistance exercise, and exercise only versus comprehensive cardiac rehabilitation). We found no evidence that exercise training either increases or decreases all cause mortality.

## Comparison with previous systematic reviews

Most previous systematic reviews of exercise training for heart failure identified insufficient number of deaths and hospitalisations to reliably comment on these outcomes.<sup>2-5,8-10</sup>

However, our finding of a statistically non-significant difference in all cause mortality with exercise training versus control is consistent with the reanalysis of individual patient data meta-analysis of the ExTraMATCH Collaborative.<sup>4</sup> More recent trials have been conducted in the context of optimal medical therapy. For example, at entry to the ACTION-HF trial 94% of patients were receiving beta-blockers and angiotension-receptor blockers or angiotensin-converting enzyme inhibitors.<sup>xxii</sup> Forty-five percent had an ICD or biventricular pacemaker implanted at the time of enrolment. Given the proven survival advantage of these medical treatments<sup>12</sup>, any incremental all-cause mortality benefit with exercise is therefore likely to be small. Based on the observed levels of mortality seen in four trials with long term follow up<sup>ii,iii,xviii,xxii</sup>, a total of some 12,000 patients would need to be randomised to exercise-based cardiac rehabilitation or usual care to demonstrate a statistically significance benefit of exercise (at 5% alpha and 80% power).

The improvements seen in HRQoL with exercise training are in accordance with the previous systematic review of van Tol and colleagues.<sup>5</sup> The recent systematic review of Chein concluded that home-based exercise training does not improve the HRQoL of heart failure patients.<sup>10</sup> Eight of the trials included in this review combined an initial period of supervised hospital based exercise training followed by a home-based programme.<sup>i,vii,x,xi,xii,xvii, xix,xx</sup> Only

one included study assessed an entirely home-based programme.<sup>ix</sup> Although we found a larger improvement in HRQoL with exercise training in those studies based solely in a hospital setting, there was a significant improvement in HRQoL compared to control in home-based exercise intervention studies.

### **Mechanism of action**

The precise mechanism through which exercise-based interventions benefits CHF remains unclear. One explanation, applicable to patients with ischaemic cardiomyopathy, is that exercise improved myocardial perfusion by alleviating endothelial dysfunction and therefore dilating coronary vessels and by stimulating angiogenesis by way of intermittent ischaemia.<sup>3</sup> Ventricular remodeling has been shown to be attenuated by exercise training.<sup>6</sup> Indeed, Belardinelli et al have demonstrated that aerobic training improves myocardial contractility and diastolic filling.<sup>16</sup> Regardless of the cause, there are important neurohormonal and musculoskeletal abnormalities in heart failure.<sup>3</sup> Exercise training may reduce adrenergic tone and increase vagal tone, as suggested by an assessment of variability of heart rate. Skeletal muscle dysfunction and wasting may also respond to exercise training. Hambrecht et al have demonstrated that regular physical activity in chronic heart failure patients stimulates vasodilatation in the skeletal muscle vasculature.<sup>17</sup>

### **Study limitations**

Although we believe this to be the most comprehensive systematic review of RCT-based evidence for the impact of exercise-based intervention on patients with heart failure to date, we acknowledge that this review has a number of limitations. The general lack of reporting methods in the included RCTs made it difficult to assess their methodological quality and thereby judge their risk of bias and potential to overestimate the effect of exercise-based interventions. However, they do not appear to be sensitive to risk of bias criteria such as intention to treat analysis and outcome bias. Although a specific goal of this review was to clarify the impact of exercise based interventions on clinical events, many included trials were relatively small and of short term follow up and there were low numbers of deaths and hospitalisations reported by the majority of the trials. In many of the studies, we identified event data in the trial descriptions of losses to follow up and exclusions rather than reported outcomes per se. Most included studies were in low to moderate risk males and included predominately (43-100%) patients with NYHA class II to III and LVEF less than 40%, with a mean age of participants across studies ranging from 43 to 72 years. The generalisability of

our findings may therefore be limited. Although the majority of evidence in this review comes from the recently reported HF-ACTION study<sup>xxii</sup>, the findings of previous trials appear consistent with this important trial.

To improve generalisability, future exercise intervention trials should include more severe CHF patients, elderly people and women and be sufficiently large and of long enough duration to accrue meaningful numbers of clinical outcomes and report these outcomes by key patient subgroups (e.g. atrial fibrillation, diabetes mellitus). There is a need to examine more community or home-based exercise intervention programmes and how such programmes can be most clinically and cost effectively integrated alongside current models of service delivery. Few of the included studies reported the actual level of exercise training undertaken by participants. Notably, the HF-ACTION study where only approximately 30% patients randomised to exercise training exercised at or above their exercise prescription.<sup>xxii</sup> Future studies therefore need to consider interventions to enhance the long term adherence to exercise training.<sup>18</sup>

## Conclusions

Compared to usual care, in low to moderate risk NYHA class II and III systolic heart failure patients, exercise-based intervention reduces heart failure-related hospitalisations and results in clinically important improvements in HRQoL. Exercise training did not reduce or increase all cause mortality. Any effect of cardiac exercise training on total mortality and HRQoL was were independent of degree of left ventricular dysfunction, type of cardiac rehabilitation, dose of exercise intervention, length of follow-up, trial quality, and trial publication date. High quality RCT and cost effectiveness evidence is needed to assess the effect of exercise training in community based settings and in more severe heart failure patients, elderly people and women.

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**Conflict of Interest**

None declared

**This paper is based on a Cochrane review first published in The Cochrane Library 2010, Issue 3 (see <http://www.thecochranelibrary.com/> for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.**



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**Figure 1. Summary of study selection**

**Figure 2a. Meta-analysis - All cause mortality <12-months follow up**

**Figure 2b. Meta-analysis - All cause mortality >12-months follow up**

**Figure 3. Meta-analysis – Hospitalisations due to heart failure**

**e-Figure 1a. Meta-analysis – All hospitalisations <12-months follow up**

**e-Figure 1b. Meta-analysis – All hospitalisations >12-months follow up**

**e-Figure 2. Meta-analysis – HRQoL: MLWHF**

**e-Figure 3. Meta-analysis – HRQoL: all scales**

**e-Figure 4. – Funnel plot – all cause mortality < 12 months**

**e-Figure 5. – Funnel plot – all hospitalisations < 12 months**

**e-Figure 6. – Funnel plot – HRQoL all scales**

## Appendix 1. Example search strategy

MEDLINE DIALOG 1950-WEEK 1 2008

1. search: myocardial-ischemia#.de.
2. search: myocard\$4 near (ischaemi\$2 or ischemi\$2)
3. search: (ischaemi\$2 or ischemi\$2) near heart
4. search: coronary-artery-bypass#.de.
5. search: coronary.ti,ab.
6. search: coronary-disease#.de.
7. search: myocardial-revascularization#.de.
8. search: myocardial-infarction#.de.
9. search: myocard\$5 near infarct\$5
10. search: heart near infarct\$5
11. search: angina-pectoris#.de.
12. search: angina.ti,ab.
13. search: heart-failure-congestive#.de.
14. search: heart near failure
15. search: 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. search: heart-diseases#.de.
17. search: (heart near disease\$2).ti,ab.
18. search: myocard\$5.ti,ab.
19. search: cardiac\$2.ti,ab.
20. search: cabg
21. search: ptca
22. search: stent\$4 and (heart or cardiac\$4)
23. search: heart-bypass-left#.de. or heart-bypass-right#.de.
24. search: 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. search: rehabilitation-centers.de.
26. search: exercise-therapy#.de.
27. search: rehabilitation.w..de.
28. search: sports#.w..de.
29. search: exertion#.w..de.
30. search: exercise#.w..de.
31. search: rehabilitat\$5.ti,ab.

32. search: physical\$4 near (fit or fitness or train\$5 or therap\$5 or activit\$5)
  33. search: train\$5 near (strength\$3 or aerobic or exercis\$4)
  34. search: (exercise\$4 or fitness) near (treatment or intervent\$4 or program\$2 or therapy)
  35. search: patient-education#.de.
  36. search: patient\$2 near educat\$4
  37. search: (lifestyle or life-style) near (intervent\$5 or program\$2 or treatment\$2)
  38. search: self-care.de.
  39. search: self near (manage\$5 or care or motivat\$5)
  40. search: ambulatory-care.de.
  41. search: psychotherapy#.w..de.
  42. search: psychotherap\$2.ti,ab.
  43. search: psychologist\$5 near intervent\$5
  44. search: relax\$6.ti,ab.
- home-based versus centre-based cardiac rehabilitation

48 / 56

45. search: relaxation-techniques#.de. or mind-body-and-relaxation-techniques#.de.
46. search: counseling#.w..de.
47. search: (counselling or counseling).ti,ab.
48. search: cognitive-therapy#.de.
49. search: behavior-therapy#.de.
50. search: (behavior\$4 or behaviour\$4) near (modify or modificat\$4 or therap\$2 or change)
51. search: stress-psychological#.de.
52. search: stress near management
53. search: cognitive near therap\$2
54. search: meditat\$4
55. search: meditation#.w..de.
56. search: anxiety#.w..de.
57. search: manage\$5 near (anxiety or depres\$5)
58. search: cbt.ti,ab.
59. search: hypnotherap\$5
60. search: goal near setting
61. search: goal\$2 near setting
62. search: psycho-educat\$5 or psychoeducat\$5
63. search: motivat\$5 near (intervention or interv\$3)

64. search: psychopathology#.w..de.
65. search: psychopathol\$4.ti,ab.
66. search: psychosocial\$4.ti,ab.
67. search: distress\$4.ti,ab.
68. search: health-education#.de.
69. search: health near education
70. search: heart adj manual
71. search: autogenic-training#.de.
72. search: autogenic\$5.ti.ab.
73. search: 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
74. search: 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
75. search: 15 or 24
76. search: 73 or 74
77. search: 75 and 76
78. search: randomized-controlled-trials#.de.
79. search: pt=randomized-controlled-trial
80. search: pt=controlled-clinical-trial
81. search: controlled-clinical-trials#.de.
82. search: random-allocation#.de.
83. search: double-blind-method#.de.
84. search: single-blind-method#.de.
85. search: (random\$ or placebo\$).ti,ab.
86. search: ((singl\$3 or doubl\$3 or tripl\$3 or trebl\$3) near (blind\$3 or mask\$3)).ti,ab.
87. search: research-design#.de.
88. search: pt=clinical-trial#
89. search: clinical-trials#.de.
90. search: (clinic\$3 adj trial\$2).ti,ab.
91. search: 77 and 90
92. search: (animals not humans).sh.
93. search: 91 not 92
94. search: limit 93 to 2001-date