

Aerobic Exercise Training in Patients With Heart Failure: A Rapid Review

Health Quality Ontario

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Evidence Development and Standards Branch at Health Quality Ontario

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Rapid reviews are completed in 2–4-week time frames. Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses. The methods prioritize systematic reviews, which, if found, are rated by AMSTAR to determine the methodological quality of the review. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (<http://www.gradeworkinggroup.org/index.htm>), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to 2 outcomes. If no systematic review is found, then RCTs or observational studies are included, and their risk of bias is assessed. All rapid reviews are developed and finalized in consultation with experts.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit <http://www.hqontario.ca> for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This rapid review is the work of the Evidence Development and Standards branch at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current as of the date of the literature search specified in the Research Methods section. Health Quality Ontario makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: <http://www.hqontario.ca/evidence/publications-and-ohnac-recommendations>.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
NYHA	New York Heart Association functional classification
SR	Systematic review

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Procedures (QBP) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Procedures initiative, visit www.hqontario.ca.

Objective of Analysis

The objective is to determine if exercise training in patients with heart failure improves survival and health-related quality of life and reduces health resource use.

Severity of heart failure is frequently reported using the New York Heart Association functional classification (NYHA), where NYHA I refers to a patient with cardiac disease but no symptoms and NYHA IV refers to a patient with severe limitations, even at rest.

The target population for this rapid review are patients discharged from hospital (or the emergency department) with heart failure. It is well established that exercise training in patients with heart failure can improve exercise capacity (1), but it is unclear if exercise training improves other outcomes such as quality of life, survival, or health resource utilization. Supervised exercise training for patients with heart failure can be offered through cardiac rehabilitation, heart failure clinic, or another structured program.

Rapid Review

Research Question

What is the effectiveness of aerobic exercise training compared to no exercise training in patients with heart failure in terms of health resource utilization, health-related quality of life, and survival?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 10, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews for studies published from January 1, 2008 to December 10, 2013. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2008, and December 10, 2013
- systematic reviews (SRs), meta-analyses, and health technology assessments
- aerobic exercise training compared to usual care
- ≥ 6 months of follow-up
- patients with heart failure and NYHA II-IV

Exclusion Criteria

- exercise training for patients with cardiac diseases, but not specifically heart failure
- non-English studies
- primary studies, grey literature

Outcomes of Interest

- health resource utilization
- survival
- health-related quality of life

Expert Panel

In December 2013, an Expert Advisory Panel on Post-Acute, Community-Based Care for CHF Patients was struck. Members of the community-based panels included family physicians, physician specialists, community health care administrators, and allied health professionals.

The role of the expert advisory panel was to provide advice on primary CHF patient groupings; to review the evidence, guidance, and publications related to defined CHF patient populations; to identify and prioritize interventions and areas of community-based care; and to advise on the development of a care pathway model. The role of panel members was to provide advice on the scope of the project, the methods used, and the findings. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the expert panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (2)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (3) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (3) For more detailed information, please refer to the latest series of GRADE articles. (3)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Rapid Review

The database search yielded 613 citations (with duplicates removed) published between January 1, 2008, and December 10, 2013. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

One systematic review met the inclusion criteria. The reference lists of the systematic review and health technology assessment websites were hand-searched to identify other relevant studies, but none were identified.

For each included study, the study design was identified and is summarized below in Table 1, a modified version of a hierarchy of study design by Goodman (1994). (4)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCTs	
Systematic review of RCTs	1
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	1

Abbreviation: RCT, randomized controlled trial.

The Cochrane systematic review by Davies et al (5) was the only systematic review identified that included the outcomes of interest (health resource utilization, mortality, health-related quality of life) of this rapid review. This systematic review had a high AMSTAR score of 9 out of a possible 11. The greatest limitation of this review was an issue of heterogeneity and whether it was appropriate to meta-analyze studies that offer such diverse exercise programs. There were many other systematic reviews identified that investigated exercise in patients with heart failure; however, these SRs primarily reported exercise capacity outcomes.

The inclusion criteria for the Davies et al (5) systematic review were limited to:

- randomized controlled trials (parallel group or cross-over design)
- adults with a diagnosis of systolic heart failure
- exercise intervention either in isolation or as a component of a cardiac program

Davies et al (5) identified 19 primary studies to include in their review; they assessed the quality of the studies and reported that the overall quality was poor. Nonetheless, Davies et al (5) meta-analyzed the studies (a brief description of the 19 studies is provided in Table 2), and it is clear that the exercise interventions varied considerably among the studies in terms of the duration of the study and the exercise, the type and frequency of the exercise, etc.

Mortality

Thirteen of the studies in Davies et al (5) reported mortality as an outcome. They did not find a significant difference in pooled mortality between the groups receiving the exercise intervention compared to those that did not. Since most of the studies had follow-up periods of <12 months, it is difficult to know the long term effects of exercise on mortality. The duration of follow-up may not have been long enough to assess significant differences in mortality.

Hospital Admissions

There were 7 studies identified in Davies et al (5) that reported hospital admissions due to heart failure. They found that when these studies were pooled, there was a significant reduction in the number of heart failure-specific hospital admissions in the group receiving the exercise intervention compared to the group receiving usual care (risk ratio 0.72, 95% confidence interval, 0.52-0.99, $P = 0.004$). When the all-cause hospital admissions were pooled, Davies et al (5) did not find a significant difference between the treatment groups.

Health-Related Quality of Life

Ten studies reported a validated health-related quality of life measure. Davies et al (5) reported that although there were different measures used to assess quality of life, quality of life was consistently rated higher in the exercise group compared to the control group. This reached significance in the 6 studies that reported health-related quality of life using the Minnesota Living with Heart Failure questionnaire ($P < 0.001$).

Table 2: Description of Studies in Davies et al (5) systematic review^a

Study	N (mean age in years)	NYHA	Exercise Type	Frequency	Duration of Study
Austin et al, 2005	200 (72)	NYHA II-III	Aerobic and resistance	2 x 2.5-hour sessions/week for 8 weeks, 1 hour/week group, 3 x 1 hour/week at home, for 16 weeks	24 weeks
Belardinelli et al, 1999	99 (56)	NYHA II-IV	Aerobic and resistance	2-3 sessions/week, 40 minutes/session; 8 weeks supervised, 12 months maintenance	14 months
Dracup et al, 2007	173 (54)	NYHA II-IV	Aerobic and resistance	4 sessions/week, 10-45 minutes/session	12 months
Giannuzzi et al, 2003	90 (60)	NYHA II-III	Aerobic	3-5 sessions/week, 30 minutes/session	6 months
Gielen et al, 2003	20 (55)	NYHA II-III (90% II)	Aerobic	7 sessions/week, 20 minutes/session	6 months
Gottlieb et al, 1999	33 (67)	NYHA II-III	Aerobic	3 sessions/week, (length of session not reported)	3 months
Hambrecht et al, 1995	22 (50)	NYHA II-III	Aerobic	4-6 sessions/week, 10-60 minutes/session	6 months
Hambrecht et al, 1998	20 (54)	NYHA II-III	Aerobic	2-6 sessions/day, 10-20 minutes/session	6 months
Hambrecht et al, 2000	73 (54)	NYHA I-III	Aerobic	6-7 sessions/week, 10-20 minutes/session	6 months
HF ACTION, 2009	2331 (59)	NYHA II-III	Aerobic	3-5 sessions/week, 15-35 minutes/session	3 months
Keteyian et al, 1996	40 (56)	NYHA II-III	Aerobic	3 sessions/week, 33 minutes/session	24 weeks
Klecha et al, 2007	50 (60)	NYHA II-III	Aerobic	3 sessions/week, 25 minutes/session	6 months
Klocek et al, 2005 (i)	42 (57)	NYHA II-III	Aerobic	3 sessions/week, 25 minutes/session	6 months
Klocek et al, 2005 (ii)	42 (54)	NYHA II-III	Aerobic	3 sessions/week, 20 minutes/session	6 months
Koukouvou et al, 2004	26 (52)	NYHA II-III	Aerobic and resistance	3-4 sessions/week, 60 minutes/session	6 months
McKelvie et al, 2002	181 (65)	NYHA I-III	Aerobic and resistance	2 sessions/week, 30 minutes/session	9 months
Mueller et al, 2007	50 (55)	NR	Aerobic	5 sessions/week, 30 minutes/session + 90 minutes walking/day	1 month
Passino et al, 2006	95 (60)	NYHA I-III	Aerobic	>3 sessions/week, 30 minutes/session	9 months
Pozehl et al, 2008	21 (66)	NYHA II-IV	Aerobic and resistance	3 sessions/week, 50 minutes/session	24 weeks
Willenheimer et al, 2000	54 (64)	NYHA mean 2.2	Aerobic/interval	2-3 sessions/week, 15-45 minutes/session	4 months

Abbreviation: NYHA, New York Heart Association functional classification.

^aThese studies are the included studies in the Davies et al (5) systematic review.

Conclusions

The results of the Davies et al (5) systematic review were generally inconclusive due to the heterogeneity and poor quality of the studies included in the review. Exercise is a life-long intervention, and these studies may not have been of a long enough duration to clearly establish changes in mortality and health resource utilization, although it would seem that with these relatively short studies there is a trend towards an improvement in health-related quality of life in patients with heart failure who receive exercise training compared to those who do not.

Based on low quality of evidence:

- There is a trend towards improved health-related quality of life in patients with heart failure who receive exercise training.
- Exercise training reduces heart failure-related hospital admissions, but did not improve survival. However, these studies may not have been long enough to assess the impact on mortality.

Acknowledgements

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Appendices

Appendix 1: Literature Search Strategies

Search date: December 10, 2013

Databases searched: OVID MEDLINE, MEDLINE In-Process, and Other Non-Indexed Citations, All EBM Databases (see below)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 2013>, EBM Reviews - ACP Journal Club <1991 to November 2013>, EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2013>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2013>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2013>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2013>, Ovid MEDLINE(R) <1946 to November Week 3 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 09, 2013>.

Search Strategy:

#	Searches	Results
1	exp Patient Discharge/	19905
2	exp Aftercare/ or exp Convalescence/	10298
3	"Continuity of Patient Care"/ or exp "Recovery of Function"/	49411
4	((patient* adj2 discharge*) or after?care or post medical discharge* or post?discharge* or convalescen*).ti,ab.	37891
5	exp Heart Failure/	93131
6	(((cardia? or heart) adj (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) adj (failure or insufficiency))).ti,ab.	135925
7	exp Pulmonary Disease, Chronic Obstructive/	26667
8	exp Emphysema/	11099
9	(copd or coad or chronic airflow obstruction* or (chronic adj2 bronchitis) or emphysema).ti,ab.	60068
10	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow* or respiratory or bronchopulmonary) adj (disease* or disorder*)).ti,ab.	37815
11	exp Pneumonia/	78260
12	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*).ti,ab.	147382
13	or/1-12	513261
14	exp Exercise Tolerance/	9966
15	exp Exercise/	127308
16	exp Rehabilitation/	162816
17	exp Rehabilitation Nursing/	1136
18	exp "Physical and Rehabilitation Medicine"/	19975
19	exp Rehabilitation Centers/	12881
20	exp Physical Therapy Modalities/	136983
21	((rehabilitat* or (physical* adj (fit* or train* or therap* or activit*)) or ((exercise* or fitness) adj3 (treatment or intervent* or program*)) or (train* adj (strength* or aerobic or exercise*)) or wellness program* or ((pulmonary or lung* or respirat* or cardiac) adj2 (physiotherap* or therap* or rehabilitat*)) or angina plan* or heart manual*).ti,ab.	235554
22	or/14-21	536336
23	Meta Analysis.pt.	52738
24	Meta-Analysis/ use mesz or exp Technology Assessment, Biomedical/ use mesz	61456
25	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	211340
26	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	2746
27	or/23-26	227857
28	13 and 22 and 27	1230
29	limit 28 to (english language and yr="2008 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	773
30	remove duplicates from 29	613

Appendix 2: Evidence Quality Assessment

Table A1: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score ^a	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Davies et al, 2010	9	✓	✓	✓	✓	✓	✓	✓	✓	?	X	✓

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews.

^aMaximum possible score is 11. Details of AMSTAR score are described in Shea et al. (2)

Table A2: GRADE Evidence Profile for Exercise Training Compared to No Exercise Training in Patients With Heart Failure

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Outcome Mortality							
13 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^b	Undetected	None	⊕⊕ Low
Outcome Hospital Admission							
7 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^b	Undetected	None	⊕⊕ Low
Outcome Health-Related Quality of Life							
10 (RCTs)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Serious limitations (-1) ^b	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^aMany of the studies had risk of bias concerns, see Table A3.

^bThe small number of events in many of the studies led to wide confidence intervals.

Table A3: Risk of Bias Among Randomized Controlled Trials for Exercise Training Compared to No Exercise Training in Patients With Heart Failure^a

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Austin et al, 2005	No limitations	Limitations ^b	No limitations	No limitations	No limitations
Belardinelli et al, 1999	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Dracup et al, 2007	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Giannuzzi et al, 2003	Limitations ^c	Limitations ^d	No limitations	No limitations	No limitations
Gielen et al, 2003	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Gottlieb et al, 1999	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Hambrecht et al, 1995	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Hambrecht et al, 1998	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Hambrecht et al, 2000	Limitations ^c	Limitations ^d	No limitations	No limitations	No limitations
HF ACTION, 2009	No limitations	No limitations	No limitations	No limitations	No limitations
Keteyian et al, 1996	Limitations ^c	Limitations ^d	No limitations	No limitations	No limitations
Klecha et al, 2007	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Klocek et al, 2005 (i)	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Klocek et al, 2005 (ii)	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Koukouvou et al, 2004	Limitations ^c	No limitations	Limitations ^e	No limitations	No limitations
McKelvie et al, 2002	No limitations	No limitations	Limitations ^e	Limitations ^f	No limitations
Mueller et al, 2007	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Passino et al, 2006	Limitations ^c	Limitations ^d	Limitations ^e	Limitations ^f	No limitations
Pozehl et al, 2008	Limitations ^c	Limitations ^d	Limitations ^e	No limitations	No limitations
Willenheimer et al, 2000	Limitations ^c	No limitations	Limitations ^e	No limitations	No limitations

^aResults are from the systematic review by Davies et al. (5)

^bBlinding was not used in this study.

^cNot clear if allocation concealment was part of the methodology of the study.

^dUnclear if blinding was used in this study.

^eUnclear if there was complete accounting of patients and outcome events.

^fUnclear if selective reporting bias was assessed.

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