UNIVERSITY of York

This is a repository copy of Cardiac rehabilitation in heart failure with reduced ejection fraction : A "should take it and not leave it" intervention.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/119728/

Version: Accepted Version

Article:

Taylor, Rod, Dalal, Hayes M, Davies, Russell et al. (4 more authors) (2017) Cardiac rehabilitation in heart failure with reduced ejection fraction : A "should take it and not leave it" intervention. American Heart Journal. ISSN 0002-8703

https://doi.org/10.1016/j.ahj.2017.07.007

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: https://creativecommons.org/licenses/

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk https://eprints.whiterose.ac.uk/

Accepted Manuscript

Cardiac rehabilitation in heart failure with reduced ejection fraction: A "should take it and not leave it" intervention

Rod Taylor, Hayes Dalal, Russell Davies, Patrick Doherty, Kate Jolly, Chim Lang, Jenny Wingham

PII:	S0002-8703(17)30206-5						
DOI:	doi: 10.1016/j.ahj.2017.07.007						
Reference:	YMHJ 5482						

To appear in: American Heart Journal



Please cite this article as: Taylor Rod, Dalal Hayes, Davies Russell, Doherty Patrick, Jolly Kate, Lang Chim, Wingham Jenny, Cardiac rehabilitation in heart failure with reduced ejection fraction: A "should take it and not leave it" intervention, *American Heart Journal* (2017), doi: 10.1016/j.ahj.2017.07.007

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Letter-to-the-Editor

Title: Cardiac rehabilitation in heart failure with reduced ejection fraction: A "should take it and not leave it" intervention

Authors:

Prof Rod Taylor (1), Dr Hayes Dalal (1), Dr Russell Davies (2), Prof Patrick Doherty (3), Prof Kate Jolly (4), Prof Chim Lang (4), Dr Jenny Wingham (1)

Affiliations:

1 Institute of Health Research, University of Exeter Medical School, Exeter, UK

2 Cardiology Department, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK

3 Department of Health Sciences, University of York, York, UK

4 School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

Corresponding Author

Name: Prof Rod Taylor

Address: Institute of Health Research, University of Exeter Medical School, Exeter, UK

Phone: +44 (0)1392 726053

Email: r.taylor@exeter.ac.uk

Letter to Am Heart Journal

Cardiac rehabilitation in heart failure with reduced ejection fraction: A "should take it and not leave it" intervention

We congratulate the HF-ACTION group on their latest publication reporting general health status from their large multicentre NIH funded randomised controlled of exercise-based cardiac rehabilitation (CR) in patients with heart failure with reduced fraction (HFrEF) (1). The accompanying editorial by Flint note that although the HF-ACTION trial achieved statistical superiority of exercise training over control in health-related quality of life (HRQoL) assessed using generic (EQ-5D) and disease-specific (Kansas City Cardiomyopathy Questionnaire (KCCQ)) measures, that these between group differences fail to achieve clinical meaningfulness as assessed by the minimally important difference (i.e. > 0.1 for EQ-5D on 0-1 scale and > 5 for KCCQ) (2).

However, we disagree with conclusion of Flint that based on the results of this one trial that "cardiac rehabilitation may be considered a "take it or leave it" option for symptomatic, stable outpatients with HFrEF". Instead the results of HF-ACTION trial needs to interpreted in the context of totality of randomised trial evidence for exercise-based CR. The most recent 2014 Cochrane review identified 33 trials that randomised 4,740 patients with predominantly HFrEF to either exercise-based rehabilitation intervention or no exercise control (3,4). The 2014 Cochrane review included the HF-ACTION study. Eighteen trials reported a validated HRQoL measure, thirteen trials reporting the Minnesota Living with Heart Failure Scale (MLwHF). A random effects meta-analysis of MLwHF data up to 12 months follow-up, showed a mean pooled improvement of -5.8 (95% CI -9.2 to -2.4) with CR compared to control (see Figure 1). Not only was this improvement in HRQoL statistically significant (P = 0.0007) but also achieved clinical meaningfulness, a difference of 5 points or larger on the MLwHF being shown to represent a clinically important difference (5). Furthermore, the Cochrane authors also showed that pooled data across all trials and across all HRQoL measures (including KCCQ findings from HF-ACTION study) was associated with mean improvement of 0.46 standard deviations (95% CI: -0.66 to -0.26, P < 0.0001) compared to control (Figure 2). Based on the baseline KCCQ scores reported in the HF-ACTION trial, a 0.5 standard deviation corresponds to a difference of 10 to 10.5 (6), exceeding the KCCQ minimally important difference of 5.

Given statistically significant and clinically important improvements in HRQoL with CR in HFrEF together with the other important benefits of reduced the risk of overall (relative risk: 0.75; 95% CI: 0.62 to 0.92, P = 0.005) and heart failure-specific hospitalisation (relative risk: 0.61; 95% CI: 0.46 to 0.80, P = 0.0004) reported by the Cochrane 2014 review, we contend that CR should be considered a "should take it and not leave it" option for symptomatic, stable outpatients with HFrEF.

Prof Rod Taylor, Institute of Health Research, University of Exeter Medical School, Exeter, UK

Dr Hayes Dalal, Institute of Health Research, University of Exeter Medical School, UK

Dr Russell Davies, Cardiology Department, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK

Prof Patrick Doherty, Department of Health Sciences, University of York, York, UK

Prof Kate Jolly, Prof Chim Lang, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

Dr Jenny Wingham, Institute of Health Research, University of Exeter Medical School, Exeter, UK.

11th May 2017

.y of Exete

References

- Ambrosy AP, Cerbin LP, DeVore AD, Greene SJ, Kraus WE, O'Connor CM, Piña IL, Whellan DJ, Wojdyla D, Wu A, Mentz RJ. Aerobic exercise training and general health status in ambulatory heart failure patients with a reduced ejection fraction-Findings from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial. *Am Heart J*. 2017;186:130-138.
- 2. Flint K. Cardiac rehabilitation in heart failure with reduced ejection fraction: A "take it or leave it" intervention. *Am Heart J.* 2017;186:127-129.
- 3. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercisebased rehabilitation for heart failure. *Cochrane Database Syst Rev.* 2014;(4):CD003331.
- Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal HM, Lough F, Rees K, Singh S, Taylor RS. Exercisebased rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart*. 2015;2:e000163.
- 5. McAllister F, Ezekowitz J, Wiebe N, et al. 106 *Cardiac resynchronization therapy for congestive heart failure.* AHRQ Evidence Report Summaries 2004:1-8.
- Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1451-9.

	Exercise			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Austin 2005	22.9	14.7	95	36.9	21.3	94	10.0%	-14.00 [-19.22, -8.78]	_ - _
Belardinelli 1999	40	19	48	51	22	46	7.3%	-11.00 [-19.33, -2.67]	_
Davidson 2010	52.9	15.7	50	56.4	18.3	42	8.3%	-3.50 [-10.54, 3.54]	
Dracup 2007	35.7	23.7	86	43.2	27.3	87	7.9%	-7.50 [-15.12, 0.12]	
Gary 2010 (comp)	24.2	16.3	15	34.3	23.6	16	4.0%	-10.10 [-24.30, 4.10]	
Gary 2010 (exalone)	25.6	19.7	17	28.9	29.9	14	2.7%	-3.30 [-21.55, 14.95]	
Jolly 2009	37.6	21	80	34.9	24.8	77	8.2%	2.70 [-4.50, 9.90]	_
Koukouvou 2004	34.1	13	16	45.2	9	19	7.9%	-11.10 [-18.65, -3.55]	
McKelvie 2002	-3.4	18.1	57	-3.3	13.9	67	9.5%	-0.10 [-5.86, 5.66]	
Nilsson 2008	23	14	35	28	20	37	7.6%	-5.00 [-12.94, 2.94]	
Passino 2006	32	26.5	44	53	32	41	4.7%	-21.00 [-33.54, -8.46]	
Witham 2012	15.4	14.8	43	11.3	12.1	44	9.5%	4.10 [-1.59, 9.79]	+
Yeh 2011	13	4	50	18	6	50	12.5%	-5.00 [-7.00, -3.00]	+
Total (95% CI)			636			634	100.0%	-5.83 [-9.21, -2.44]	•
Heterogeneity: $Tau^2 = 22.85$; $Chi^2 = 40.24$, $df = 12.(P < 0.0001)$; $P = 70\%$									
$T_{1} = (1 + 0.0001) + (1 + 0.0001)$									-20 -10 0 10 20

Figure 1. Pooled Minnesota Living with Heart Failure score up to 12 months follow up

Test for overall effect: Z = 3.37 (P = 0.0007)

Favours expercise Favours control

Figure 2. All quality of life scores up to 12 months follow up.

	Ex	ercise		C	Control		Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Austin 2005	22.9	14.7	95	36.9	21.3	94	6.2%	-0.76 [-1.06, -0.47]	+
Belardinelli 1999	40	19	48	51	22	46	5.5%	-0.53 [-0.94, -0.12]	
Bocalini 2008	-87	4	22	-81	6	20	4.0%	-1.17 [-1.83, -0.51]	- -
DANREHAB 2008	-42.7	9.1	19	-37.4	11.4	15	3.8%	-0.51 [-1.20, 0.18]	
Davidson 2010	52.9	15.7	50	56.4	18.3	42	5.5%	-0.20 [-0.62, 0.21]	-+
Dracup 2007	35.7	23.7	86	43.2	27.3	87	6.2%	-0.29 [-0.59, 0.01]	
Gary 2010 (comp)	24.2	16.3	15	34.3	23.6	16	3.7%	-0.48 [-1.20, 0.23]	
Gary 2010 (exalone)	25.6	19.7	17	28.9	29.9	14	3.7%	-0.13 [-0.84, 0.58]	
HF ACTION 2009	72.39	20.46	906	71.24	21.48	850	7.1%	0.05 [-0.04, 0.15]	t
Jolly 2009	37.6	21	80	34.9	24.8	77	6.1%	0.12 [-0.20, 0.43]	+
Jónsdóttir 2006a	-47.55	8.7	21	-44.1	14.04	20	4.2%	-0.29 [-0.91, 0.32]	+
Klocek 2005 (Const)	-109	23.5	14	-71.7	23.5	7	2.4%	-1.52 [-2.57, -0.48]	
Klocek 2005 (Prog)	-99	23.5	14	-71.7	23.5	7	2.6%	-1.12 [-2.10, -0.13]	
Koukouvou 2004	34.1	13	16	45.2	9	19	3.7%	-0.99 [-1.69, -0.28]	
McKelvie 2002	-3.4	18.1	57	-3.3	13.9	67	5.9%	-0.01 [-0.36, 0.35]	+
Nilsson 2008	23	14	35	28	20	37	5.2%	-0.29 [-0.75, 0.18]	-+
Norman 2012	-81	18.2	19	-77.9	11.6	18	4.1%	-0.20 [-0.84, 0.45]	-+-
Passino 2006	32	26.5	44	53	32	41	5.3%	-0.71 [-1.15, -0.27]	
Willenheimer 2001	-0.7	0.8	20	0	1	17	3.9%	-0.76 [-1.44, -0.09]	
Witham 2005	-69	13	36	-65	10	32	5.1%	-0.34 [-0.82, 0.14]	
Yeh 2011	13	4	50	18	6	50	5.5%	-0.97 [-1.39, -0.56]	
Total (95% CI)			1664			1576	100.0%	-0.46 [-0.66, -0.26]	•
Heterogeneity: Tau ² = 0.14: Chi ² = 94.85 df = 20 (P < 0.00001); P = 79%									
Test for overall effect: $7 = 4.58$ (P < 0.00001)								-4 -2 0 2 4	
restion overall effect. 2	4.50 (i	- 0.0U	,001)						Favours exercise Favours control