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## 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

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## 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.

11<sup>th</sup> May 2017

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

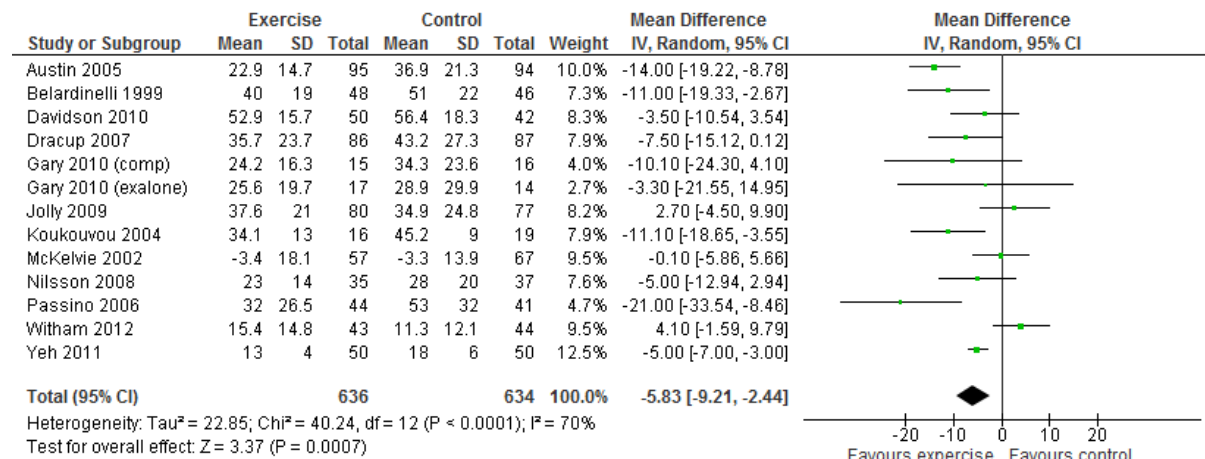


Figure 2. All quality of life scores up to 12 months follow up.

