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Group Title: Effect of training on peak oxygen consumption in patients with heart failure with preserved ejection fraction

To the Editor: Given the limited success of drug therapies for patients with heart failure with preserved ejection fraction (HFpEF), physical inactivity, low fitness, and obesity are promising modifiable targets for the management of HFpEF.1

The impressive OptimEx-Clin trial2 demonstrated a statistically significant improvement in cardiorespiratory fitness with high-intensity and moderate continuous training compared with controls at 3 months, however, no significant effects remained at 12-month follow-up. Consequently, the authors concluded that this lack of improvement in cardiorespiratory fitness did not support either training regimen for patients with HFpEF. We encourage caution with this interpretation.

The clinical benefits of exercise training are acquired through more than cardiorespiratory fitness alone. Indeed, increases in cardiorespiratory fitness are not obligatory for improvements in cardiovascular risk factors,3 and exercise-mediated cardioprotection is partly explained through improved (cardio)vascular function.4 Therefore, the failure to achieve the *a priori* primary endpoint of a peak VO2 increase of 2.5 mL/kg/min does not rule out a clinical benefit of exercise training in patients with HFpEF. In our recent retrospective cohort study5 including 18,485 patients with HFpEF, exercise-based cardiac rehabilitation was associated with significantly lower odds of all-cause mortality (OR 0.65, 95% CI 0.60-0.71), compared to 1:1 propensity-matched HFpEF controls at 2-year follow up.

The limitations of this retrospective cohort study are obvious,5 but warrant a more cautious interpretation of the results presented by Mueller et al. For example, the proportion of acute coronary syndrome in the exercise training groups (5.8%) was lower than in the control group (8.3%). Whilst the OptimEx-Clin trial is underpowered for this outcome, there is similarity in effect size with our retrospective cohort study where exercise-based cardiac rehabilitation associated with lower 2-year mortality compared to controls (9.3% versus 15.2%).

Collectively, the OptimEx-Clin trial provides new insights into exercise training for patients with HFpEF, however, the absence of a “clinically meaningful effect size” on cardiorespiratory fitness does not necessarily translate to an absence of clinically meaningful effect. Therefore, randomized clinical trials are needed to substantiate the role of exercise training (moderate- or high-intensity) for patients with HFpEF on clinically relevant outcomes, such as morbidity and mortality.

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**Conflict of Interest Disclosure**s: Dr Buckley reports receiving research funding from Bristol-Myers Squibb (BMS)/Pfizer. Dr Lip reports being a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No other disclosures were reported.

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