Title: OUTSTEP-HF: re-evaluating the role of physical activity measures in drug and device development in heart failure

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One of the hallmarks of the syndrome of heart failure (HF) is a reduction in exercise tolerance and limitation in physical activity. Patients with HF have been reported to be approximately half as active as healthy individuals, with a similar weekly physical activity level as those with multiple sclerosis and a greater degree of limitation than those with chronic obstructive pulmonary disease (COPD).[1] This impairment in physical activity is negatively correlated with quality of life, promotes deconditioning, sedentary behaviour and frailty, and has prognostic implications with lower levels of physical activity associated with an increased risk of both HF hospitalisation and mortality.[2]

Understanding the effects of a pharmacological or device therapy on measures of physical activity and cardiorespiratory fitness has thus been of great interest across medical disciplines, including HF. Indeed, it has been suggested that therapies that safely improve intermediate measures reflecting how patients feel and function may be considered for regulatory approval by the US Food and Drug Administration (FDA).[3,4] Established methods of assessing physical functioning include measures of peak exercise capacity and cardiorespiratory fitness (with 6-minute walk distance [6MWD] testing or peak oxygen uptake [peak VO_2] on cardiopulmonary exercise testing), device-based metrics of physical activity (using wearable or implantable health technologies), and global integrated measures of health-related quality of life (HRQOL).

In an effort to provide further information regarding the incremental benefits of neprilysin inhibition to renin-angiotensin system inhibition alone in patients with HF and reduced ejection fraction (HFrEF), the randOmized stUdy Using accelerometry to Compare Sacubitril/valsarTan and Enalapril in Patients With Heart Failure (OUTSTEP-HF) was designed to evaluate the short-term effects of sacubitril/valsartan, compared with enalapril,

on physical activity over 12 weeks of treatment with a co-primary endpoint of change from baseline in 6MWD (a measurement of functional capacity) and change from baseline in non-sedentary daily activity measured using a wearable accelerometer (a measurement of functional performance).[5] Eligible patients had a left ventricular ejection fraction of 40% or less, were in New York Heart Association (NYHA) functional classification II-IV, and had elevated natriuretic peptide levels. As detailed in the results now published by Piepoli and colleagues in the *European Journal of Heart Failure*, 621 patients were randomised, of whom approximately half had NYHA functional class III/IV symptoms, and the majority were receiving guideline directed medical therapy with 92% taking a beta-blocker, 77% a diuretic and 67% an MRA.[6] Target doses of sacubitril/valsartan and enalapril were achieved in 66% and 80% of patients, respectively.

Compared with enalapril, sacubitril/valsartan did not have any significant beneficial effect on either of the two co-primary endpoints. Mean 6MWD at baseline was approximately 370m and this increased in both treatment groups at 12-weeks with a between-treatment difference for sacubitril/valsartan versus enalapril of 8.98 m (97.5% confidence interval [CI] -1.31, 19.27; p=0.0503). Similarly, there was no significant between-group differences in non-sedentary daily activity as measured by accelerometery (−6.14 minutes [97.5% CI −25.70, 13.41; p=0.48]. Of note, despite the increase in 6MWD in both treatment arms at 12-weeks, the level of non-sedentary daily activity decreased in both treatment arms from a baseline of approximately 510 minutes, a much greater level of activity than that expected by the investigators who powered the study for a 10% change from a baseline of 200-230 minutes. There were no significant differences in any of the other reported metrics of physical activity after 12-weeks of treatment.

The neutral findings of OUTSTEP-HF are similar to those reported recently with sacubitril/valsartan in the AWAKE-HF trial using a different accelerometer-based metric of physical activity.[7] Even if modest improvements in 6MWD in OUTSTEP-HF were suggested, between-group changes fell below traditionally accepted clinically meaningful thresholds for improvement. Discordant longitudinal changes in 6MWD and accelerometer-derived physical activity further highlight the complexity of interpretation of these intermediate measures. How are we to reconcile the neutral results of these trials with the results of PARADIGM-HF where there was clear evidence of significant improvements in morbidity and mortality as well as in quality of life, physical function and symptom burden?[8] Moreover, do these results further our understanding of measurements of physical activity limitation in HF and their potential role as endpoints in therapeutic development?

When considering these endpoints as potential surrogates for morbidity and mortality outcomes, several key considerations must be taken into account (Figure): the surrogate must have a biologically plausible relationship with the outcome; there must be consistent evidence of association between the surrogate and the outcome; and finally, there must be consistent evidence from randomised trials that the degree of change in a surrogate with an intervention is correlated with the treatment effect on a clinically-relevant outcome.[9] The association between functional limitation, HF severity, and prognosis is well established.[2] Cross-sectional assessments of physical activity, cardiopulmonary fitness, and sedentary time have been shown to predict incident HF events.[10] It is biologically plausible that a treatment which improves physical activity may reduce the risk of worsening HF events or mortality, however the largest randomised trial of exercise training in HFrEF, HF-ACTION, failed to show a significant benefit in improving outcomes despite improvements in cardiopulmonary exercise duration and peak VO_2.[11] Furthermore, discordant results between a treatment's effect on

measurements of physical activity and its effect on morbidity and mortality have been shown for multiple therapies, raising the question regarding the suitability of these as surrogate endpoints in HF. Therapies such as vagal nerve stimulation, flosequinan and ibopamine have been shown to have beneficial effects on exercise capacity but to have neutral or, in the case of flosequinan and ibopamine, harmful effects on morbidity and mortality outcomes. Indeed, with the exception of cardiac resynchronization therapy, none of the pillars of HFrEF therapy have shown consistent beneficial effects on measurements of physical activity or exercise capacity.[12] More recently, several small randomized clinical trials have failed to demonstrate significant improvement in 6MWD or accelerometer-derived physical activity with the sodium-glucose cotransporter 2 (SGLT2) inhibitors compared with placebo, despite their established benefits in preventing HF events and extending event-free survival.[13,14]

In a meta-analysis of pharmacotherapy or device trials, no significant correlation was observed between a treatment's short-term effects on peak VO_2 or 6MWD and the long-term effect on mortality seen in randomised controlled trials.[15] Unlike indices of left ventricular remodelling and NT-proBNP where there is established correlation between a treatment's effect on these measurements and the effect on clinically-relevant HF endpoints, the lack of such correlation for measures of exercise capacity such as 6MWD draws into question their suitability as sole surrogate markers for outcomes in patients with HFrEF.[16,17] Indeed, it has been suggested that their use as a surrogate marker is predicated on congruent changes in other markers such as natriuretic peptides, HRQOL measures, or left ventricular volumes.[3]

Although the 6MWD test has the attraction of being cheap and easily integrable into clinical trials it does have several limitations. The result is effort dependent and can also be influenced by encouragement from the test administrator. As such, it can be problematic in

open-label settings and in trials in which partial unblinding may occur (for instance, with a study intervention with unique, identifiable side effects). Furthermore, it is subject to cardiac and non-cardiac limitations that do not necessarily reflect HF status. In contrast to 6MWD or other single time-point measurements of exercise capacity or physical activity, the use of wearable or implantable accelerometers has the attraction of allowing continuous measurements over prolonged periods, which may facilitate a more complete and accurate assessment of the effect of a treatment on a patient's functional capacity. Whilst levels of physical activity are correlated with other markers of HF severity in both HFrEF and HFpEF, the relationship between changes in these measurements and outcomes is less well established. In the NEAT-HFpEF trial, no correlation was seen with the degree of change of physical activity measured by accelerometer and the observed change in markers of HF severity including NYHA functional classification, 6MWD and KCCQ scores.[18] Indeed, in OUTSTEP-HF, 6MWD increased in both treatment groups while measured daily activity decreased, potentially representing an overestimation of baseline activity despite a 2-week baseline epoch and a regression to usual activity levels by patients over the 12-week follow-up. The use of continuous measurements of physical activity as a surrogate endpoint in HF may also be limited by several factors. Changes in measured daily activity are reliant on significant behavioural change as patients with HF may be accustomed to a sedentary lifestyle and such adaptations may take longer to establish than the relatively short follow-up of trials such as OUTSTEP-HF, limiting the ability of such trials to detect differences in physical activity levels. Longer follow-up however in OUTSTEP-HF would have been considered unethical given the established clinical benefits of sacubitril/valsartan. Moreover, patients with HF are often elderly and frequently have multiple comorbidities such as coronary artery disease, COPD, stroke, diabetes, peripheral vascular disease, neurocognitive

conditions, and arthritis which may limit their physical activity levels despite improvements in their HF status.

What role therefore do these endpoints have? The use of endpoints such as 6MWD may be limited to interventions which may be expected to more directly improve these metrics such as cardiac rehabilitation and exercise training. Such improvements may not necessarily improve morbidity and mortality but may nevertheless facilitate important changes for patients in their global HF status. A significant correlation between improvements in exercise capacity and measurements of HRQOL was observed in a meta-analysis of studies of exercise-based cardiac rehabilitation programmes, although an improvement in 6MWD of 80m was estimated to be required to predict a significant improvement in HRQOL, over twice the 35m change which OUTSTEP-HF was powered to detect and which is generally considered as a clinically meaningful change in HF.[19] Identification of patient subgroups who may more favourably respond with respect to physical activity, cardiorespiratory fitness, and limiting sedentary time remains an active area of investigation.

The lack of significant change in 6MWD or measured physical activity levels with sacubitril/valsartan in OUTSTEP-HF should not be perceived as a negative finding and dissuade clinicians from using this life-saving medication in eligible patients with HFrEF. Furthermore, the neutral findings with regards to 6MWD and accelerometer measured activity levels highlights the potential limitations of these metrics as surrogate endpoints. A substantial body of evidence now exists supporting the clinical benefits in HFrEF of so-called "quadruple therapy" with a combined neprilysin and angiotensin receptor inhibitor in addition to a beta-blocker, mineralocorticoid receptor antagonist and SGLT2 inhibitor along with device therapy, when indicated. As clinicians, we owe it to our patients to promote

adoption of these therapies which improve symptoms, extend meaningful survival and prevent hospitalisation, even in the absence of evidence of benefit on endpoints such as those examined in OUTSTEP-HF.

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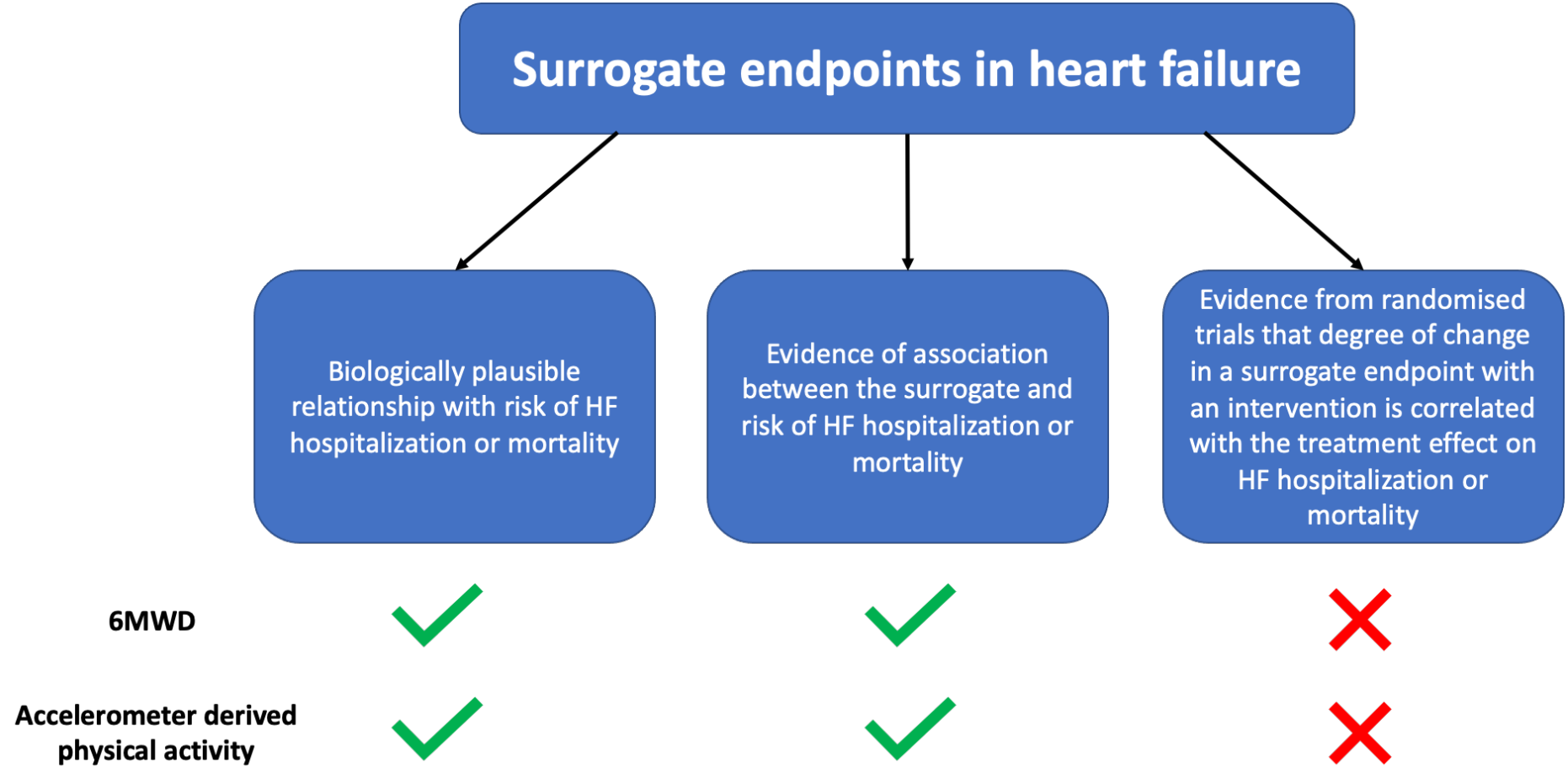
Figure: Key criteria to establish validity of surrogate endpoints in heart failure



Abbreviations: HF, heart failure; 6MWD, 6-minute walk distance.