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EDITORIAL COMMENT

Step by Step

Really Need It in Our World*

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Actigraphy is a means of quantifying physical movement often conceptualized as counting steps. It is typically assessed using wrist or hip-worn digital accelerometers that are ubiquitous in cellular phones and watches. However, despite its appeal as an easily acquired real-world patient-focused functional measurement, perhaps with the ability to improve equity by reaching patients historically unable to be enrolled in clinical trials due to remote care, actigraphy remains an incompletely realized clinical and research tool and only a potential regulatory approval endpoint.[1] Although actigraphy appears to have face value as an estimate of patient activity and has been highlighted as a promising clinical outcome assessment by clinicians, researchers, and regulators, it has not been successfully employed to detect a benefit for a clinical intervention. A review of 11 randomized clinical trials in patients with heart failure (HF) that incorporated actigraphy as an outcome found haphazard variability in study construction and actigraphy implementation, and no study of pharmacological therapy was able to demonstrate an improvement on an actigraphic endpoint.[2] In part, it is believed these failures occurred because actigraphy remains dramatically unvalidated and unstandardized with regard to quantification, context of use, and interpretation.

Actigraphy will need multiple concurrently generated broad swaths of evidence to manifest as a comprehensible and reliable HF clinical and research instrument. Step 1, as elaborated by the Heart Failure Collaboratory-Academic Research Consortium, terminology and reporting features will need to be standardized.[1] Step 2, as an extension, preferred methods of implementation will need to be established, such as how to wear the devices. Step 3 requires validation that these accelerometers and their digitally processed movement "counts" actually measure activity and that this measured activity has clinical relevance; 1 way to evaluate this sort of content validity is by testing for convergent validity, meaning does actigraphy align with other clinical measures such as health-related quality of life or functional assessments such as exercise tests. Step 4, like other clinical outcome assessments, actigraphy must be shown to be consistent, reproducible, and stable over time. Step 5, actigraphy will need to be able to detect change, or differences between patients treated or not treated with an intervention, and the magnitude of change that is clinically significant will need to be defined.[3]

In this issue of *JACC: Heart Failure*, Golbus et al[4] have engaged in convergent validity analyses to better understand the clinical meaning and relevance of actigraphic measurements, as described under step 3 earlier. Golbus et al[4] use the data from the CHIEF-HF (Canagliflozin: Impact on Health Status, Quality of Life, and Functional Status in Heart Failure) clinical trial, in which patients with HF were randomized to canagliflozin or placebo. Enrolled almost entirely during the COVID-19 pandemic, CHIEF-HF was a decentralized clinical trial that enrolled 476 patients with smartphones and had a primary endpoint of change in health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) after 12 weeks of treatment.[5] The KCCQ is a validated HF instrument to measure health-related quality of life, and was captured on patients' mobile

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phones. The trial was stopped early by the industry sponsor as a business decision; however, the primary endpoint of the KCCQ total symptom score was significantly better after 12 weeks with canagliflozin treatment, with mean difference of 4.3 points better than placebo (95% CI: 0.8-7.8; $P = 0.016$). Actigraphy in CHIEF-HF was assessed with the commercially available Fitbit Versa 2 device that was provided to each patient, quantified by daily mean activity counts during 2-week eras at the beginning and end of the 12-week study period.

Golbus et al[4] assessed the convergent validity between actigraphy and quality of life by anchoring the accelerometer-derived mean daily step counts to KCCQ scores. They reported that 89% of the patients had complete actigraphic and KCCQ data, and 41% had a reduced left ventricular ejection fraction. Golbus et al[4] found that increasing 25-point ranges of KCCQ total symptom and physical limitation subscores, scores consistent with better health-related quality of life, had progressively higher daily step counts and greater numbers of mean floors climbed. The patients with KCCQ scores of 0 to 25 had mean daily step counts around 2,300 to 2,400 steps, whereas those with KCCQ scores of 75 to 100 and the best reported health status had mean daily step counts of 4,900 to 5,300.

Nonetheless, the continuous associations between step count and KCCQ scores were nonlinear, even when adjusted for clinical characteristics. With the baseline step count and KCCQ assessments there appeared to be a linear increase in KCCQ scores with increasing mean daily step counts until an inflection point around 5,000 steps daily, after which there was little further increase in KCCQ. In other words, mean daily step counts over 5,000 steps were not associated with better KCCQ scores, whereas step counts decreasing under 5,000 correlated with lower KCCQ scores. These data suggest that there may be a ceiling effect of step count with regard to how it is connected to patient-reported quality of life; perhaps above 5,000 steps daily there is a disconnect between activity and perceived health status, and perhaps this is a limitation to using actigraphy to assess patient well-being.

However, the association between change in step count at 12 weeks and the corresponding change in KCCQ score may be more informative for how actigraphy would assess a therapeutic intervention. Again, there was a nonlinear association. A comparative decrement in mean daily step count over the 12 weeks was not associated with a decline in KCCQ score, whereas an increase in mean daily step count was associated with a linear increase in KCCQ score. The generally accepted clinically significant improvement in KCCQ of approximately 5 points was associated with an increase of approximately 2,000 mean steps daily, which may be an early estimate for minimal clinically detectable improvement in actigraphy for this population. It is not clear why a decrease in step count was not associated with a drop in KCCQ score, but it may suggest that these 2 tools do not capture the same concepts or aspects of the patient experience and that there is not convergent validity for worsening.

These data thus demonstrate that actigraphy appears to assess experiences that affect patient-reported health status and reinforces that actigraphy may be a viable clinical outcome. In contrast, the association appears to have limitations, and the KCCQ and actigraphy unsurprisingly do not reliably assess the same components of the patient experience. Additionally, in the context of these data, it is notable that the treatment effect of canagliflozin seen on the KCCQ score in the primary CHIEF-HF analysis was not detectable by actigraphy, undermining its potential sensitivity to detect change. There was no detectable difference in mean daily step counts between patients treated with canagliflozin or placebo, mean difference 30 steps (95% CI: −284 to 344).[5] Actigraphy as described by daily mean step counts was unable to detect a difference between the populations, highlighting that step 5 as described earlier remains unattained. Based on that analysis, it is not clear whether canagliflozin failed to improve functional status or whether some other component of actigraphy, such as maximal step count, walking speed, timed maximal distance, or other assessment scheme, might have better detected a difference.

In conclusion, these data are part of a large body of necessary and incremental work that will be required for actigraphy to attempt to achieve its potential as a patient-centered and efficient measure of functional status. Golbus et al[4] have thankfully moved our understanding of actigraphy forward, although it is still the new kid on the block and will require substantial further testing and validation before widespread reliable clinical and research use.

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