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Function Follows Form

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The phrase "forms follows function" was coined by Louis Sullivan (1) in 1896 to describe how architecture design should reflect the purpose of the building. As stated by Sullivan, "all things in nature have a shape, that is to say a form, an outward resemblance, that tells us what they are;.unfailingly, in nature these shapes express the inner life, the native quality." This fact holds true for clinical trials. Their form or design reflects the scientific evolution, the "inner life," created by preceding studies that led to the current design. HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) exemplifies the premise of form following function. The protocol was based on a series of phase 2 clinical trials identifying a potential benefit of exercise training in patients with heart failure with reduced left ventricular ejection fraction (HFrEF). In all these protocols, participants were required to be in stable condition, defined as not having a recent cardiovascular hospitalization. Thus, HF-ACTION was designed as an outpatient intervention requiring at least 6 weeks of medical stability.

The domino effect of a clinical trial's design cannot be underestimated. The translation of trial results into professional guidelines, U.S. Food and Drug Administration approvals, and reimbursement policies–the "function"–flows from the "form" of pivotal clinical trials. Function follows form. As HF-ACTION was the largest clinical trial evaluating the impact of exercise training on patients with HFrEF (2), it is not surprising that, on February 18, 2014, the Centers for Medicare and Medicaid Services (CMS) expanded coverage of cardiac rehabilitation (CR) to patients with stable, chronic heart failure, defined as patients with symptomatic HFrEF on optimal heart failure therapy and without any recent (≤6 weeks) or planned (≤6 months) major cardiovascular hospitalizations or procedures (3).

In this issue of *JACC: Heart Failure*, the down-stream effects of HF-ACTION and the CMS coverage decision on clinical practice are explored by Pandey et al. (4). The investigators

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examine the use of CR among Medicare beneficiaries with HFrEF in 2 cohorts: those with recent heart failure hospitalizations (n = 11,696) and those with only outpatient visits (n = 11,832). The analysis revealed very low use of CR (4.3%) after hospitalization and even lower use when patients were seen only in the outpatient setting (2.2%). Although the period of analysis corresponded with the first 2 years after the CMS coverage decision, and a significant improvement in CR use for the hospitalized cohort was identified (from 2.8% to 5.0%; $p < 0.001$), the levels of use are surprisingly low given the inclusion of HF-ACTION results in guidelines in 2011.

Would the use of CR be improved if HF-ACTION had been designed as an immediate post-discharge intervention and CMS coverage began immediately? The low rate of referral (approximately 10% in 2014) may have continued to follow the positive trajectory noted prior to the CMS decision, but the required delay makes it easier to push off these decisions to patients' outpatient providers. Unfortunately, we know that providers resist making changes to patients' treatment in the outpatient setting even when mandated by a protocol (5). Thus, it is not surprising to see the even lower rate of use of CR among patients with only outpatient visits. Inpatient stays are a window of opportunity to initiate treatments and educate patients. However, given the low use of CR for indications that allow immediate initiation of CR post-discharge, it is likely that other structural issues exist that go beyond the design of HF-ACTION.

A significant driver for underuse is the structure of our health care system. The existence of a CR program at the hospital at which a patient with HFrEF was admitted increased the likelihood of using CR by 2-fold in the present analysis. The focus on inpatient care over prevention has challenged our ability to implement clinical strategies in the outpatient setting. The limited reimbursement for cardiovascular services from payers prevents the maintenance of enough CR programs to meet even a fraction of the demand (6). There are an estimated 4,160 CR programs in the United States for an estimated 1.25 million potential participants. The lack of availability is creating CR deserts; it is hard to use something that is not available. Strategies such as virtual CR using telehealth platforms, many of which have been implemented during the coronavirus disease 2019 pandemic, may hold promise of increasing availability and access.

Even if patients were to be referred, beneficiaries must pay an out-of-pocket cost per session to participate. For those on fixed incomes or without significant savings, the cost of participation can be too high. Reflecting back to HF-ACTION, which covered the cost of CR as part of the study protocol, participation in facility-based training was close to the protocol-specified target. Similar to improving cardiovascular medication adherence, full coverage of CR would likely have an immediate impact on participation and address racial and ethnic disparities in use.

The disparities noted in the present study for sex and race serve as a reminder that the issues we have witnessed this year in terms of both social justice and the disproportionate impact of coronavirus disease 2019 on communities of color are systemic and infiltrate all aspects of care. Some of these may be driven by socioeconomic factors such as program availability and copayments, but time and time again, we see results such as those in

the present analysis. Bias exists in medicine. Education and transparency achieved by publishing these results are important parts of addressing disparities. The next step is implementing systematic strategies such as those highlighted by the Million Hearts program (https://million-hearts.hhs.gov/tools-protocols/tools/cardiacrehabilitation.html). By reducing the opportunity for bias to influence decisions and treatment opportunities, we can start to make headway in correcting years of inequity.

Learning from one's past is an important lesson for anyone. Like the continued evolution of architecture, clinical trials have an opportunity to improve in order to obtain better function. A core group of HF-ACTION investigators identified a number of opportunities to improve on the "form" of an exercise training trial and designed the REHAB-HF (Rehabilitation Therapy in Older Acute Heart Failure Patients) trial (7). In addition to addressing the 6-week delay in initiating CR, the study included patients with heart failure independent of left ventricular ejection fraction and targeted older patients. As with HF-ACTION, the design reflects the previous work of a number of investigators, so again form is following function. Time will tell if function will follow form.

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