

EDITORIAL COMMENT

Hospitalizations and Prognosis in Elderly Patients With Heart Failure and Preserved Ejection Fraction



Time to Treat the Whole Patient*

Dalane W. Kitzman, MD,[†] Bharthi Upadhyya, MD,[†] Gordon Reeves, MD[‡]

In the comic strip *Peanuts*, Charlie Brown allows his optimism and narrow focus to override his repeated objective experiences. He rushes at the football, only to have Lucy yank it away while he is in perfect midkick. Charlie launches into the air and falls, defeated again. This could be an appropriate metaphor for our approach to date to heart failure (HF) with preserved ejection fraction (HFpEF), the dominant form of HF in elderly persons. It seemed logical to assume that in patients selected for HF, cardiac factors would be the dominant if not the sole contributor to pathophysiology and the key to effective therapy. However, after more than 2 decades of research pursuing this paradigm, the objective evidence suggests that HFpEF is far more complex and that a broader view is needed.

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In this issue of *JACC: Heart Failure*, Carson et al. (1) report valuable insights regarding outcomes in elderly patients with HFpEF, bolstering the need for

a broader HFpEF paradigm. The investigators used the database from I-PRESERVE (Irbesartan in Heart Failure and Preserved Ejection Fraction), a well-designed, well-conducted, multicenter, international trial. The minimal age was 60 years, recognizing that HFpEF is overwhelmingly a disorder of elderly persons. Despite appropriate inclusion criteria and sample size, long treatment duration and follow-up, good adherence and retention, and successful blood pressure reduction with irbesartan, there was no treatment-related difference in any clinical outcome. Subgroup analyses also produced negative results. Of the 5 large multicenter end point trials in HFpEF to date, all were neutral on their primary end points. However, unlike other trials, I-PRESERVE did not find a trend for reduced hospitalizations. Thus, as a truly neutral trial, I-PRESERVE provides a particularly valuable, robust database to examine many clinically important questions regarding HFpEF pathogenesis and prognosis.

Carson et al. (1) found that during >4 years of follow-up, 5,963 all-cause hospitalizations occurred in the cohort (n = 4,128). Overall, hospitalizations and rehospitalizations were frequent and prolonged, associated with much higher mortality, and due to multiple causes. Although not reported, much worse quality of life and higher health care costs were also likely. These data underscore the high burden of HFpEF in elderly patients.

Remarkably, only about 20% of hospitalizations were for HF (1). Furthermore, although 53.6% of hospitalizations were cardiovascular, when considering stroke, transient ischemic attack, peripheral vascular, and “unknown” causes separately, hospitalizations for noncardiac causes (49.6%) exceeded those for

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From the [†]Section on Cardiovascular Medicine, Department of Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina; and the [‡]Division of Cardiology, Department of Medicine, Sidney Kimmel Medical College at Thomas Jefferson University School of Medicine, Philadelphia, Pennsylvania. This work was supported in part by grants R01AG189165, R01AG045551, and P30AG021332 from the National Institutes of Health. Dr. Kitzman is a consultant for Abbvie, GlaxoSmithKline, Relypsa, Regeneron, DC Devices, and Actavis; has received grant funding from Novartis; and owns stock in Gilead Sciences and Relypsa. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

cardiac causes (47.7%). Recurrent hospitalizations were frequent; however, even among patients whose first hospitalizations were for HF, most subsequent hospitalizations were for non-HF causes. Compared with those not hospitalized, subsequent mortality was high (hazard ratio: 4.86) in the relatively few patients initially hospitalized for HF. However, this was not much higher than in patients with initial non-HF hospitalizations (hazard ratio: 4.25).

These data confirm that in the elderly HFpEF population, non-HF hospitalizations dominate, and a large proportion of overall deaths are noncardiac. This conclusion is validated by the consistency of these observations in several other HFpEF databases, including that of Ather *et al.* (2) who found a similarly high proportion of non-HF admissions and deaths among patients with HFpEF, and significantly more than in HF with reduced ejection fraction (HFrEF) (3). These data should not reignite the debate regarding whether HFpEF is “real HF,” because non-HF indications also constitute the majority of hospitalizations in elderly patients with HFrEF (3). The data should also not be interpreted to indicate (as some have suggested) that somehow trials enrolled the “wrong” patients, because in not only this but virtually all other studies, even among patients with HFpEF whose initial hospitalizations were for HF, most subsequent hospitalizations were for non-HF indications (3). Instead, a fitting interpretation of these findings is that HFpEF pathophysiology and outcomes may differ somewhat from that initially hypothesized, suggesting the need for a revised paradigm.

A classic principle of geriatrics may help explain both the diversity of outcomes in elderly patients with HFpEF and their poor prognosis after either HF or non-HF hospitalizations. In elderly patients hospitalized primarily for a specific disorder, many factors other than that single disorder or organ system strongly influence outcomes (4). These can include advanced age, globally reduced organ system reserve capacity, physical frailty, impaired cognition, and comorbidities (often numerous and severe). In HFpEF, noncardiac comorbidities are particularly common, more so than in HFrEF, and are a strong independent predictor of hospitalization and prognosis (2). These considerations are consistent with the emerging paradigm of HFpEF as a systemic disorder, which is increasingly supported by several lines of evidence (5). Given such a multifactorial, complex milieu, it is not surprising that drugs and interventions aimed primarily at a single organ system have repeatedly failed to strongly affect overall outcomes in HFpEF.

Among the formidable combination of factors listed here, physical frailty and cognitive dysfunction are particularly noteworthy. Frailty is often present even when elderly patients with HF are at their chronic, stable baseline (6), and physical function worsens further when an acute illness (such as HF decompensation) develops. The hospital environment—with immobilization, fasting, sleep deprivation, and disorientation—can dramatically worsen physical frailty with rapid, severe loss of muscle mass and function (4). Indeed, frailty and physical function are strong, independent predictors of adverse outcomes in HF and elderly patients in general (7). In elderly hospitalized patients, cognitive dysfunction is common, often unrecognized, complicates management, and contributes to all-cause adverse outcomes. Furthermore, in patients with HF specifically, declines in physical and cognitive function are linked (8).

At the time when elderly hospitalized patients with HF are routinely discharged—after the resolution of congestion and control of rhythm, rate, and blood pressure—their multiple comorbidities, globally reduced organ reserve, severe physical deconditioning, and cognitive dysfunction remain unaddressed (4). The result is the “post-hospitalization syndrome,” with high rates of rehospitalization, mortality, and nursing home admission, prolonged physical disability, poor quality of life, and high health care costs (9).

How can we improve outcomes in elderly hospitalized patients with HFpEF? Attending solely to the cardiovascular features of HFpEF appears unlikely to strongly influence all-cause outcomes. Progress will likely require innovative multidisciplinary team approaches that recognize the importance of noncardiac factors, assess them objectively, and implement measures to mitigate their adverse effects (4). For example, total comorbidity burden can be quantified with simple scales. Physical function and frailty can be quickly assessed without special equipment using clinically available information and the standardized, reproducible Short Physical Performance Battery, a strong, independent predictor of rehospitalization, death, and nursing home admission in hospitalized elderly patients. Cognitive function can also be quickly assessed at bedside with well-validated surveys. Each of these provides actionable information for designing individualized interventions (4).

Given these considerations, what kinds of novel interventions are promising? Application of an established acute care for elders geriatric care model, either as a multidisciplinary team or a sequestered unit, significantly improves key outcomes in acutely

hospitalized elderly patients (4,10). One component of this model that appears most robust is early rehabilitation to address physical function impairments (10). Hospitalized older patients with HF frequently have impaired strength, balance, and mobility as well as endurance. Of note, exercise training trials in chronic, stable patients with HFpEF have shown uniformly positive results, with improved physical function and usually enhanced quality of life (11). This improvement appears to occur primarily through noncardiac mechanisms, such as improved arterial and skeletal muscle function, which are impaired in HFpEF and contribute to physical dysfunction and adverse clinical outcomes (11). However, when cardiac rehabilitation was recently approved for Medicare reimbursement for chronic stable HFpEF, patients with HFpEF were explicitly excluded, as were hospitalized and recently hospitalized patients with HF. REHAB-HF (A Trial of Rehabilitation Therapy in Older Acute Heart Failure Patients), a recently launched, National Institutes of Health-funded clinical trial (NCT02196038) seeks to address these critical evidence gaps (7).

The report by Carson et al. (1) provides a critical clue regarding the optimal timing of interventions aimed at breaking the cycle of the post-hospitalization syndrome in elderly patients with HF (1). They found a 30-day readmission rate of 18%, in line with national statistics for elderly patients with HF, helping validate this dataset. Importantly,

they also found that post-hospitalization events were highest in the first 30 days and returned toward baseline after 6 months. This pattern of enhanced early post-hospitalization risk was first reported 25 years ago by Pernenkil et al. (12) in elderly patients with HF, confirmed later specifically in patients with HFpEF, and is observed in virtually all HF populations. This suggests that interventions should start as early as feasible after hospital admission and continue during this high-risk period. Interventions should also be targeted to prevent initial hospitalizations (6).

Although continuing the search for ways to improve cardiovascular function and outcomes in patients with HFpEF, these data suggest that a fruitful approach will be to develop novel strategies to treat the whole patient. Such an approach is not only consistent with a wide range of emerging data and a view of HFpEF as a systemic disorder, it is also in accord with an enduring principle of medical therapy. Charlie Brown focused singularly on the football and overlooked the capricious person holding it. To make progress in HFpEF, we may need to focus not only on the heart but also on the frail body that contains it.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Dalane W. Kitzman, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, North Carolina 27151-1045. E-mail: dkitzman@wakehealth.edu.

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