JACC: CARDIOVASCULAR IMAGING
VOL. 11, NO. 1, 2018
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2017.08.010

EDITORIAL COMMENT

The Changing Face of Heart Failure*

James E. Udelson, MD

It has been just over 3 decades since the initial reports of the effect of vasodilators and angiotensin-converting enzyme inhibitors on outcomes of patients with heart failure with reduced ejection fraction (HFrEF) (1,2). Continued progress in incrementally improving outcomes over the ensuing decades has been little short of stunning, as we have progressively seen the institution of beta-adrenergic blockers, angiotensin receptor blockers, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and devices. A recent network meta-analysis quantified the incremental effects of the therapeutic strategies in terms of mortality reduction (3). The combination of a beta-adrenergic blocker, a mineralocorticoid receptor antagonist, and angiotensin receptor-neprilysin inhibition was associated with an estimated 63% reduction in all-cause mortality relative to putative placebo. The data illustrate truly remarkable progress, and substantiate the generally accepted notion that once left ventricular (LV) dysfunction is present in a patient with heart failure, the predominant pathophysiological driver of progression and clinical outcome is neurohormonal activation (as reviewed by Udelson and Stevenson [4]).

In the early 1970s, some attention began to focus on diastolic pathophysiology (5), and subsequently, clinical investigators began to describe the phenotype of what is now commonly referred to as heart failure with preserved ejection fraction (HFpEF). As an example, in 1983, Dougherty et al. (6) found that ~one-third of a group of 188 patients with HF undergoing radionuclide ventriculography had ejection fraction (EF) ≥45%. Echocardiographic left atrial emptying index was abnormal, suggesting a noncompliant LV. Hospital- or medical center-based studies of patients with HF referred for imaging of LV function revealed a broad range of prevalence of preserved EF in such patients, but community-based epidemiological studies were fairly uniform in the estimation of ~50% prevalence of HFpEF among those with HF (7,8).

Given the therapeutic advances across the spectrum of cardiovascular diseases, as well as the aging of the population, an interesting aspect of the ongoing HF story is the temporal trend in the underlying substrate for the clinical HF syndrome. Owan et al. (9) examined temporal trends in the prevalence of reduced versus preserved EF among patients hospitalized with decompensated HF at Mayo Clinic hospitals from 1987 through 2001. Among over 4,500 hospitalized HF patients with available EF data, the prevalence of HFpEF increased over those years, reaching 50% to 60% in the later years. Consistent with current thinking about the importance of comorbidities and the cardiometabolic/inflammatory milieu in the pathophysiology of HFpEF (10), the rates of hypertension, atrial fibrillation, and diabetes increased over time, coincident with increasing HFpEF prevalence.

It is important to note that these data were based on patients who were hospitalized for HF. There are some advantages to studying such a population, in that the HF diagnosis is relatively certain given the severity of signs and symptoms that prompt hospitalization. However, the data may not be representative of those diagnosed with HF who are community-dwelling and have not been hospitalized. HF hospitalization is a sentinel event, often representing an inflection point signifying a more unfavorable disease trajectory. More recently, Gerber et al. (11) reported on trends in HF incidence and outcomes from 2000 to 2010. In this report, some community-based HF was captured, as ~one-third of the patients were diagnosed with HF as outpatients. Similar to the fully hospitalized population sample, across that decade, the proportion with HFpEF increased.

Thus, there is a gap in our understanding of longer-term trends in the underlying functional correlates of fully community-based patients with HF. The paper

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Division of Cardiology and the CardioVascular Center, Tufts Medical Center, Boston, Massachusetts. Dr. Udelson has reported that he has no relationships relevant to the contents of this paper to disclose.

by Vasan et al. (12) in this issue of *iJACC* goes a long way toward filling that gap. The authors interrogated the highly annotated database of the Framingham study across 3 decades from 1985 through 2014, to examine trends in the prevalence of LV dysfunction in both asymptomatic subjects and in those with HF, as well as subsequent outcomes and risk factor profiles. There were several important findings. The prevalence of asymptomatic LV dysfunction by echocardiography decreased across the decades, from ~3.4% to 2.2%, although the risk of incident HF or death following identification of LV dysfunction was stable. Among those outpatients who were newly diagnosed with HF, the prevalence of HFrEF decreased, whereas the prevalence of HFpEF

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increased. Across the decades, outcomes following diagnosis of HFrEF improved, but outcomes associated with HFpEF were unchanged. The prevalence of the "new" category of HF with midrange EF (40% to 50%) remained stable over time (at ~13%), as did outcomes associated with that phenotype. Better treatment of hypertension and decreased prevalence of MI explained a substantial proportion of the reduced prevalence of asymptomatic LV dysfunction, and changes in risk factor profiles were significantly associated with the increasing HFpEF prevalence.

There are substantial strengths to the analysis, including the decades-long consistent capture of data in one of the world's leading long-term epidemiological studies, and the consistent application of their diagnostic criteria for HF, which the Framingham study investigators have validated over time. Framingham authors always mention the relative population homogeneity as a limitation, requiring conformation in more multiethnic populations. However, high proportions of HFpEF have been reported in cross-sectional studies in different age groups (8), countries (13), and racial groups (14), so although the exact proportions may vary, the concepts and importance of focusing attention on HFpEF remain.

Why are these data important? As noted in the previous text, substantial therapeutic progress has been made for patients with HFrEF across the decades spanned by the paper by Vasan et al. (12). This is not true for HFpEF, for which no effect on natural history has been seen in at least 8 large, randomized, controlled outcome trials involving thousands of patients. The consistent reports of increasing HFpEF prevalence among HF inpatients from 1987 to 2001 (9), among a mixed in- and out-population from 2000 to 2010 (11), and now for community-dwelling outpatients with newly diagnosed HF from 1985 to 2014 (12) all represent the changing face of HF. The data substantiate the importance of ongoing focus and effort to find therapies that will have a favorable effect on this growing group of patients. As some have noted, this effort may require more informed pathophysiological phenotyping to enable better targeted therapeutics to improve outcomes (10). A complimentary or alternative approach would focus therapeutic efforts more prominently on symptoms of everyday life and functional capacity, ensuring safety but not focusing on long-term outcomes (15). Either way, the results presented by Vasan et al. (12) strongly support the critical nature of the effort and the potential effect on both populations and individuals.

ADDRESS FOR CORRESPONDENCE: Dr. James E. Udelson, Division of Cardiology and the CardioVascular Center, Tufts Medical Center, Box 70 Cardiology, 800 Washington Street, Boston, Massachusetts 02111. E-mail: JUdelson@tuftsmedicalcenter.org.

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KEY WORDS echocardiography, ejection fraction, epidemiology, heart failure