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Age Disparities in Heart Failure Research

Dr. Dalane W. Kitzman, MD and **Dr. Michael W. Rich, MD**
Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Dr Kitzman); and Department of Internal Medicine, Washington University School of Medicine, St Louis, Missouri (Dr Rich)

In the united states, heart failure (HF) affects more than 5 million individuals, accounts for nearly $40 billion in annual health care expenditures,[1] is associated with severely increased morbidity, mortality, and reduced health-related quality of life, and is the only major cardiac disorder that is increasing. Importantly, HF is overwhelmingly a disorder of the older population. Heart failure prevalence increases inexorably from middle to old age, with no abatement even into the tenth decade of life. It is the most common reason for hospitalization among Medicare recipients, and its lethality and complications increase progressively with age.[2]

Despite the enormous public health implications of HF, there has been little progress during the past 20 years in improving HF outcomes.[3] This may in part reflect an inherent age bias in HF research. Indeed, the most common form of HF (ie, HF with a preserved ejection fraction [HFPEF]) is almost exclusively a disorder of persons aged 60 years or older.[4] However, HFPEF was not even generally accepted as a genuine form of HF until around 2004, and even today its nomenclature remains controversial. Between 1985 and 2004, intensive research on the form of HF most common among middle-aged persons (HF with reduced ejection fraction [HFREF]) led to completion of approximately 100 randomized clinical trials, including more than 50 000 participants. In contrast, during this same period, only 1 large clinical trial was reported in patients specifically with HFPEF. As of 2010, only 4 trials regarding persons with HFPEF have been reported, and none have had positive results.[5] Although evidence-based guidelines for treatment of HFREF are extensive, little evidence is available for HFPEF. [6]

Perhaps not surprisingly, the prognosis of HFPEF has worsened during the past decade and the prognosis for HFREF has improved.[3] Furthermore, there is no redress of this disparity in sight, because only 1 large US multi-center National Institutes of Health (NIH)–funded trial that addresses HFPEF is ongoing, while several trials are addressing HFREF. In addition, pharmaceutical and device companies may be reluctant to fund HFPEF trials, given the failure of previously published studies to produce positive results.

Even though older adults are most commonly affected by HFREF, there is also a remarkable age disparity in HFREF research. Most early trials that established angiotensin-converting enzyme inhibitors as first-line therapy to reduce mortality in HFREF excluded patients older than 75 or 80 years.[7] In a review of HFREF trials through 2002, the average age of enrolled patients was 59 years, nearly 20 years less than the average age of persons with HFREF in

Corresponding Author: Dalane W. Kitzman, MD, Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157 (dkitzman@wfubmc.edu).

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the general population.[7] Although some recent trials have had higher or no upper age limits, there has been relatively little improvement. For example, in the HF-ACTION trial published in 2009,[8] the mean age of participants was 59 years, only 18% were 70 years or older, and only 5% were of the average age of persons with HFREF in the general population. This discrepancy occurred despite the absence of an upper age limit and encouragement from study leadership and NIH staff to strive for higher recruitment of elders.

Thus, eliminating upper age limits in HF trials is only a start. To correct this situation, proactive measures are needed. The NIH could require that investigators include expected age ranges of participants in grant applications and progress reports and insist on clearly defined plans to enroll persons in age ranges relevant to the specific disease as it occurs in the general population. A similar step, enacted in 1993, played a substantial role in addressing the disparities in medical research in women and minorities.[7] An NIH requirement would likewise lead to allocation of resources and expertise to address age disparities. Another important step for studies in this population would be to evaluate outcomes of functional ability and return to community after discharge, outcomes generally not assessed in younger age groups.

With appropriate resources and focus, identification, recruitment, and retention of older persons in clinical trials are feasible. The physical, sensory, and cognitive impairments common in older persons can be overcome with reasonable accommodations, including large-font informed consent documents, hearing assistance, improved accessibility to study sites, transportation to study visits, and provision for targeted home visits. These and other measures have already been effective for large NIH-sponsored trials.[9]

Often, comorbidities are the rationale for excluding older persons in clinical trials, based on the argument that the disease must be isolated in its “pure” form to study it. However, multiple comorbidities are one of the key characteristics of HF in the older population. Patients with HF in the Medicare database have more than 4 to 5 comorbidities per patient, whereas younger patients have only 1 to 2.[10] Furthermore, these comorbidities often drive a large portion of the adverse outcomes observed in older persons.[10] In the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE) trial,[5] the majority of clinical events were related to comorbidities rather than to HF. Continuing to design studies that exclude or ignore comorbidities fails to address the realities of HF as it exists in the general population.

Several recent, large multicenter trials have reversed the age bias. The ELITE (Evaluation of Losartan in the Elderly) and I-PRESERVE trials had a minimum age for entry of 60 years,[5] as does the current NIH-funded trial, TOPCAT (Trial of Preserve Cardiac Function Failure With an Aldosterone Antagonist). However, this approach is crude and fails to address the problem of excluding older patients due to common coexisting conditions. Insisting that trial recruitment plans and resources reflect the disorder as it exists in the population would be a fair and easily administered mandate. The US Food and Drug Administration could (and should) follow suit. In addition, such a proposal is well aligned with the current Department of Health and Human Services strategic framework for optimizing health and quality of life for patients with multiple chronic conditions. Investigators may initially object to such a requirement, as in 1993 when the NIH mandated attention to inclusion of women and minorities in trials. However, investigators quickly learned how to achieve the new goals, as they would for age-appropriate inclusions.

In addition, research proposals should be expected to carefully justify each exclusion for comorbidities and discuss how inclusion of patients with comorbidities would cause harm to

participants or to study integrity. Currently, the often long list of exclusions receives relatively little scrutiny by grant reviewers. When changes are recommended, it is usually to add more exclusions, rather than to challenge investigators to consider ways to broaden the enrolled population and ensure the results are generalizeable. This is important because published clinical trials apply to a minority of patients seen in an HF clinic. Eliminating noncritical exclusions would have the added benefit of enhancing rate of enrollment, which has emerged as a major challenge in US-based clinical trials.[5]

This approach would lead to new insights into diseases that can be immediately applied to helping the patients who are primarily affected by them. No longer would clinicians have to wonder whether a newly released medication or device is applicable to the typical patients seen in their practices. Researchers should support such a move. The current system lacks integrity when it uses public funds to produce research results that do not apply to a large majority of the population affected. Future trials should do better, and a modest investment in effort and cost could yield great dividends.

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