JACC: HEART FAILURE VOL. 6, NO. 8, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Of Probabilities and Uncertainties

Current Challenges of the Heart Failure Epidemic*

Véronique L. Roger, MD, MPH

"Medicine is a science of uncertainty and an art of probability."
— Sir William Osler (1)

Over the past 2 decades, major efforts have been dedicated to the investigation of the heart failure (HF) epidemic. The ultimate goal of such investigations is to reduce the burden of disease through prediction, prevention, and effective management of HF.

Unquestionably, these efforts have moved the field forward. Progress has been made in the conceptualization of HF as a chronic condition characterized by acute exacerbations, which trigger periodic hospital admissions such that HF is the leading cause of hospitalizations in the United States. Focus has been brought to the requirement that, to investigate the HF epidemic, one must apply sound epidemiology principles and accurately ascertain HF including defining the critical point that each episode is truly the first one to occur, in order to be considered incident. Population denominators are necessary to calculate rates. Getting this information requires access to data from longitudinal cohorts, which are part of a defined population and can be followed over time. Using these rigorous epidemiologic methods, the Framingham Heart Study and the Olmsted County Study demonstrated through similar approaches that, until the turn of the century, the incidence of HF was mostly stable while survival was improving. The chief implication of these findings was that the HF epidemic was mainly an epidemic of hospitalizations as more survivors became candidates for recurrent hospitalizations (2,3). Over the last decade, there is evidence that the incidence of HF is beginning to decline, particularly for HF with reduced ejection fraction (EF), with no change in mortality (4). There is also evidence that the hospitalization curve has been bent at least for HF as a primary cause of hospitalizations. The heterogeneous nature of HF has been recognized because HF is not a disease, but rather a syndrome classified according to the left ventricular EF into HF with reduced EF (HFrEF) or HF with preserved EF (HFpEF). The proportion of HFpEF has been increasing over time and it is now the dominant presentation of HF.

These reports, and several more that space constraints preclude reviewing, have greatly improved the understanding of HF. In doing so, this body of research also uncovered important challenges with regards to the very nature of HF and its presentation. These must now be addressed to sustain progress in the fight against the epidemic. A major issue is that the HFpEF phenotype is incompletely understood. There is ample evidence that HFpEF itself is heterogeneous, such that HFpEF is really a syndrome within the HF syndrome. Three phenotypes have been proposed: 1) younger patients with diastolic dysfunction; 2) overweight patients with diabetes and obstructive sleep apnea; and 3) older patients with chronic kidney disease, myocardial remodeling, pulmonary hypertension, and right ventricular failure. These descriptive phenotypes are helpful to begin to characterize the clinical case mix of patients. However, because these categories overlap, their mechanistic implications are limited, and the pathophysiology of the syndrome HFpEF remains ambiguous. Most importantly, no study to date has demonstrated any survival benefit for any treatment in HFpEF. Because this therapeutic vacuum pertains

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

From the Department of Cardiovascular Diseases and Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota. Dr. Roger has reported that she has no relationships relevant to the contents of this paper to disclose.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.05.003

to the now dominant form of HF, progress against the epidemic is stalled.

In this issue of *JACC: Heart Failure*, Tsao et al. (5) report data from the Framingham Heart Study and the Cardiovascular Health Study, on HF incidence and mortality between 1990 and 1999 and 2000 to 2009.

SEE PAGE 678

Of particular interest is the focus on the type of HF and the shift in case mix between HFpEF and HFrEF. Using documentation from the medical record, HF was classified as HFrEF if the EF was <50%, or HFpEF if the EF was ≥50%. A large proportion of patients could not be classified because there were no imaging data to document EF close enough in time to the HF episode to reliably classify it. The results indicated that the overall incidence of HF did not change across the 2 time periods, whereas the proportion of HFpEF gradually increased over time. These findings are consistent with prior reports, a consistency that is important because it clearly supports the generalizability of data obtained in different populations (4).

The paper by Tsao et al. (5) raises significant points of broad relevance to epidemiology studies. The importance of studying diverse populations in other cohorts is appropriately underscored by the authors given the predominance of white persons in Framingham and Cardiovascular Health Study. To this end, recent data from the National Inpatient Sample and from the ARIC (Atherosclerosis Risk In Communities) study (6,7) describe an alarming disparity of the burden of HF among black persons, with a gap that is widening over time. Hence, the present paper further emphasizes the need to study diverse populations. To address this need, new studies are required and new methods need to be deployed. The paper by Tsao et al. (5) raises another important point that pertains to the ascertainment of HF. The diagnosis relied on clinical ascertainment and was adjudicated using information from the medical record. As clinicians know well, the diagnosis of HF can be difficult for several reasons. HF often presents with comorbidities, and the symptoms and signs of HF may be atypical and can be mimicked by comorbidities, such as respiratory disease and/or obesity. In patients with high body mass index, assessing volume status is often quite challenging leading to uncertainties with regards to the mere diagnosis of HF. This diagnostic ambiguity is amplified in the setting of HFpEF where several coexisting conditions are often present, possibly partially causal and often confound the diagnosis. The report by Tsao et al. (5) reminds us of the urgency to define and deploy deep phenotyping for HFpEF in order to progress in the understanding of what has become the dominant proportion of HF cases.

As acknowledged by the authors, a notable number of patients did not undergo cardiac imaging studies within a time frame that would allow using these clinical data to classify the episode in HFrEF or HFpEF. Thus, the reported trends in case mix and the sex-specific patterns are conceivably impacted by confounding by indication. The observation of uneven documentation in medical records informs the interpretation of other studies relying on medical records where the same limitations related to missing data undoubtedly apply, but do not always get adequate attention. Hallmark challenges encountered when using medical records for research include missing data and biases related to variations in care-seeking behaviors and in clinical practice. It is important to be reminded of these issues at a time of rapid growth in the implementation of electronic health records, which considerably expand the availability of clinical datasets for research. Because these new data sources represent unprecedented opportunities for broader and more efficient data collection, there is considerable interest into their use for epidemiology research, referred to as “electronic epidemiology.” Unlike primary data collection in epidemiologic research, health records data are collected for the clinical episode and are directly influenced by the patient’s health status and care seeking behavior, and by clinician’s care practices and documentation. Hence, the patient and provider, not the researcher, determine the time of observation that directly has an impact on inference that can be drawn from the results. Large-scale collection of data as enabled by digital technology and electronic medical records cannot be expected to be immune to limitations and biases inherent to data generated in the course of care. Far from reducing uncertainty, reliance on electronic health records can in fact amplify it because large numbers will get us closer to the magical threshold of 0.05 without lessening bias or minimizing confounding by indication. Relying on these large and broader datasets obtained from medical records requires a deliberate commitment to methodologic rigor consistent with the fundamentals of epidemiology. For example, data science approaches can address the uneven nature of clinical documentation intrinsic to medical records data. Deep learning methods can be applied to handle missing data and gradient-boosting machines can build risk prediction models that forego the need for complex imputation. The application of

these methods to electronic medical record research must be promptly deployed and widely disseminated to generate scientifically valid results.

Hence, the paper by Tsao et al. (5) constitutes a call to action by underscoring the importance of continued study of the HF epidemic. It commendably illustrates the complexity of this charge including emerging challenges that the scientific community must address in order for this important journey to remain as rewarding in the next decades as it has been in previous ones.

ADDRESS FOR CORRESPONDENCE: Dr. Véronique L. Roger, Department of Health Sciences Research, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: roger.veronique@mayo.edu.

REFERENCES

1. Brainyquotes. Sir William Osler quotes. Available at: https://www.brainyquote.com/quotes/william_osler_159326. Accessed May 9, 2018.

2. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–402.

3. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292:344–50.

4. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996–1004.

5. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. J Am Coll Cardiol HF 2018;6:678–85.

6. Ziaeian B, Kominski GF, Ong MK, et al. National differences in trends for heart failure hospitalizations by sex and race/ethnicity. Circ Cardiovasc Qual Outcomes 2017;10:e003552.

7. Chang P, Wruck L, Shahar E, et al. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005-2014): the Atherosclerosis Risk in Communities (ARIC) Study Community Surveillance. Circulation 2018;138:12–24.

KEY WORDS ejection fraction, epidemiology, heart failure, incidence, mortality, trends