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EDITORIAL COMMENT

Cardiac Amyloidosis

More Than a Needle in a Haystack*

Karen E. Joynt Maddox, MD, MPH,[a,b] Kathleen W. Zhang, MD[a]

Cardiac amyloidosis has emerged as an underdiagnosed cause of heart failure (HF) that is associated with significant morbidity and mortality, particularly in later stages of disease (1,2). Small, single-center studies have estimated the prevalence of cardiac amyloidosis at 13% among patients with HF with preserved ejection fraction, including among those hospitalized for HF (3,4). Wild-type transthyretin cardiac amyloidosis has been detected in 13% to 16% of patients with severe aortic stenosis referred for transcatheter aortic valve replacement (5,6) and is also associated with carpal tunnel syndrome (7). Significant advances in noninvasive diagnostic testing (8,9) and targeted amyloid therapeutics (10) have piqued clinical enthusiasm for diagnosing cardiac amyloidosis; however, diagnostic delays of up to 34 months persist (11,12). The scope and consequences of cardiac amyloidosis underrecognition are poorly characterized both from the clinical outcomes perspective and from the policy and reimbursement perspective, with potentially important implications for both.

In this issue of *JACC: CardioOncology*, Arora et al. (13) report on their examination of the prevalence of HF hospitalization for cardiac amyloidosis and associated in-hospital mortality and 30-day readmission rates from January 2010 to August 2015 using the Nationwide Readmissions Database. HF hospitalizations for cardiac amyloidosis were identified as those with a primary diagnosis of HF and a secondary diagnosis of amyloidosis by International Classification of Diseases-Ninth Revision codes; amyloidosis type was not specified in the database. HF hospitalizations with amyloidosis were matched 3:1 to nonamyloidosis HF hospitalizations, and rates of in-hospital mortality and 30-day readmission were compared between patients hospitalized for HF with and without amyloidosis. Among 1,593,360 HF hospitalizations included in the study, 2,846 (0.18%) were coded as being associated with amyloidosis. Rates of in-hospital mortality and 30-day readmission were 4% and 22%, respectively, in the entire matched cohort. In analyses adjusted for sociodemographics and comorbidities, amyloidosis was associated with a higher likelihood of in-hospital mortality (odds ratio: 1.46; 95% confidence interval: 1.17 to 1.82) and 30-day readmission (odds ratio: 1.17; 95% confidence interval: 1.05 to 1.31), driven by noncardiovascular readmissions.

This study confirms in a national, administrative database that cardiac amyloidosis is significantly underdiagnosed among patients admitted with decompensated HF and is associated with worse short-term clinical outcomes. It also suggests that a national effort is needed to better care for these patients, who are at high risk for missed diagnosis and treatment.

Treatment for amyloidosis has evolved significantly over the past several years (10). As a result, timely diagnosis is even more critical to allow treatment initiation in earlier stages of disease, when inhibition of amyloid fibril formation has greater clinical benefit. Currently available therapies include transthyretin stabilizers and transthyretin synthesis inhibitors for transthyretin amyloidosis, chemotherapy and stem cell transplantation for light chain amyloidosis, and cardiac transplantation for selected patients with advanced HF (14). Tafamidis, which is approved for the treatment of transthyretin cardiac amyloidosis, was shown to reduce both all-cause mortality and cardiovascular hospitalizations in the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin

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From the [a]Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA; and the [b]Center for Health Economics and Policy, Institute for Public Health, Washington University School of Medicine, St. Louis, Missouri, USA.

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Cardiomyopathy) trial (15), showing its potential to have meaningful effects on HF hospitalization and readmission outcomes over time.

The findings of Arora et al. also have implications for health policy. The Hospital Readmissions Reduction Program, enacted in 2010, penalizes hospitals with high 30-day hospital readmission rates for patients with HF, among other target conditions. Hospitals that care for high proportions of patients with amyloidosis may be at a disadvantage under this program because HF etiology is not taken into account when assessing hospital performance. Patients with light-chain amyloidosis, in particular, are at increased risk for malnutrition due to gastrointestinal autonomic dysfunction (16), refractory anasarca due to nephrotic syndrome and right heart failure, and non-cardiovascular readmissions due to adverse effects of chemotherapy and should not be held to the same 30-day readmission standards as a typical patient with HF. Similarly, the Hospital Value-Based Purchasing Program, which awards bonuses and imposes penalties in part on the basis of performance on HF mortality rates, could inappropriately judge hospital performance if amyloid prevalence is not considered.

Additionally, it is likely that specific protocols and quality measures needed to improve diagnosis, reduce mortality, and mitigate readmission in patients with cardiac amyloidosis differ from those for typical patients with HF. These may include specific treatment guidelines (and exclusion from HF guideline therapies that may not benefit this population), better integration of care across medical disciplines as well as between specialty amyloidosis centers and local care providers, and better coordination with outpatient cancer care and infusion centers.

Finally, as diagnosis and management for patients with cardiac amyloidosis continue to evolve, ongoing attention to their outcomes is crucial. An updated analysis of the National Readmissions Database in the current era of noninvasive diagnostic testing and targeted amyloid therapeutics will be useful to assess for interval change in cardiac amyloidosis prevalence and outcomes among HF admissions. Although clinically driven efforts to improve physician education have likely improved recognition of cardiac amyloidosis among attentive clinicians, hospital systems-driven efforts to ensure appropriate HF hospitalization reimbursement may help bring early diagnosis of cardiac amyloidosis to the forefront of everyday clinical practice.

AUTHOR DISCLOSURES

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ADDRESS FOR CORRESPONDENCE: Dr. Karen E. Joynt Maddox, Cardiovascular Division, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8086, St. Louis, Missouri 63110, USA. E-mail: kjoyntmaddox@wustl.edu. Twitter: @kejoynt.

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