EDITORIAL COMMENT

The Evolving Epidemiology of Amyloidosis*

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Systemic amyloidoses are group of (rare) protein misfolding diseases causing organ dysfunction due to progressive deposition of insoluble amyloid fibril deposits (1). The heart is one of the most common organs involved, followed by the kidneys, liver, and nervous system. The 2 most prevalent types are immunoglobulin light chain (AL) amyloidosis and wild-type transthyretin (wtATTR) amyloidosis. The diagnosis of amyloidosis is often serendipitous on a tissue biopsy or imaging. Paucity of awareness, symptoms overlapping with those caused by more common disorders, and lack of a single confirmatory diagnostic test contribute to delays in diagnosis. Histological demonstration of amyloid deposition remains the gold standard. The very high sensitivity of bone scintigraphy agents for cardiac transthyretin amyloid (ATTR) deposits has allowed for noninvasive diagnosis of cardiac ATTR amyloidosis (2).

In this issue of *JACC: CardioOncology*, Westin et al (3) report the experience from the Danish national registry of a change in epidemiology of cardiac amyloidosis (CA) in Denmark. Of the 619 patients with CA, the median age increased from 67.4 years in 1998-2002 to 72.3 years in 2013-2017 with a 4% increase in the frequency of male patients. The incidence of CA increased from 0.88 to 3.56 per 100,000 person-years in the Danish population ≥65 years old. Whereas CA carried a significantly higher mortality than the control population, the 2-year

mortality decreased from 82.6% (95% confidence interval: 69.9%-90.5%) to 50.2% (95% confidence interval: 43.1%-56.9%).

In this study, there was approximately 1 year in delay from onset of symptoms to diagnosis, with the clinical presentation including that of heart failure, cardiomyopathy, atrial fibrillation, or pacemaker implantation. The delay in diagnosis has remained an unfortunate theme for patients with amyloidosis. For cardiac amyloidosis, features on an echocardiogram such as loss of longitudinal systolic function, a thick-walled left ventricle (LV) without accompanying hypertension, and normal or low voltages on the electrocardiogram in a patient with apparent LV hypertrophy are all important early clues. Ordering the appropriate confirmatory next investigation is equally important. Imaging with a bone scintigraphy agent (3,3-diphosphono-1,2-propanodicarboxylic acid/hydroxymethylene diphosphonate/pyrophosphate) for ATTR deposits allows for noninvasive diagnosis of cardiac ATTR amyloidosis (2). However, lack of cardiac uptake on a bone scan does not rule out CA and may result in costly delay in diagnosis of cardiac AL amyloidosis. Cardiac magnetic resonance imaging, with appropriate abnormal gadolinium kinetics, is very specific for diagnosis of amyloidosis but has a very limited role in differentiating AL from ATTR amyloidosis. Until a universal amyloid specific tracer (ie, forbetapir or florbetaben) becomes routinely available, a combination of cross-sectional cardiac imaging (echocardiography or cardiac magnetic resonance) and bone scintigraphy, along with testing for a monoclonal protein in blood and urine, is needed to avoid diagnostic errors and delays.

The presence of carpal tunnel syndrome in a patient with heart failure is an important clue to the presence of wtATTR amyloidosis. In the study from Westin et al (3), approximately 10% of patients had

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history of carpal tunnel syndrome (often needing multiple surgical corrections) compared to just over 1.8% in the control population. Carpal tunnel may present 5 to 9 years before the diagnosis of clinical ATTR CA; thereby offering clues to early screening (4). Whereas the true prevalence of cardiac ATTR in those with "idiopathic" carpal tunnel remain unknown, wider recognition of this association is a critical clue in the early diagnosis.

Westin et al (3) show a progressive improvement in outcomes of the patients with CA from 1-year mortality of 74% in 1998-2002 decreasing to 39% in 2013-2017 cohorts with improvement also reported at 5 years. There are impressive yet sobering statistics with poor survival beyond 5 years. Other studies in AL amyloidosis also show that survival has significantly improved from a median of 1.5 years for patients diagnosed in late 1990s to more than 5 years in contemporary cohorts (5). Most studies on outcomes of ATTR amyloidosis essentially track the natural history of the condition because of the lack of any effective treatments until recently (6). Inability to accurately identify the amyloid type is a major limitation of the current study and differences in case mix may have contributed to the change in outcomes.

Availability of disease modifying therapies can lead to increased enthusiasm for consideration of amyloidosis in the differential diagnosis. There has been remarkable progress in treatment of ATTR amyloidosis. Treatment with tafamidis (an agent that stabilizes the transthyretin molecule) shows improved survival in cardiac ATTR amyloidosis (7). ATTR lends itself to gene targeting due to the apparent lack of critical need for transthyretin in human physiology—from silencing RNA to the first study of gene editing agent as a single shot "curative" treatment (8). Daratumumab (a monoclonal antibody directed to CD38) in combination with chemotherapy has become the first licensed treatment for AL (9). However, none of the currently available therapies or even those in trials (for ATTR amyloidosis) help to reverse the damage—a

crucial missing step in a disease where deaths continue to occur despite highly efficient treatments which reduce/stop amyloid deposition. Moreover, all the approved treatments for amyloidosis are expensive (tafamadis costs ~$225,000/year and daratumumab ~$200,000/year in the United States). These costs must be re-evaluated to make drugs widely available in countries with limited health care resources.

The true prevalence of CA is unknown. In this study, the incidence of CA increased from 0.88 to 3.56 per 100,000 person-years in the Danish population ≥65 years old. It may be more common as reported recently by a Swedish group—20% of heart failure with thickened LV wall had amyloidosis giving a population incidence of 1.1% or 1:6000 (10). With more than half a billion persons projected to be aged 80 years or older by 2050, a substantially larger population will be at risk of developing cardiac ATTR amyloidosis and will also have higher risk of monoclonal gammopathies (11); hence, increasing the risk of developing AL amyloidosis. The ever-increasing incidence and recognition make amyloidosis a new global health care problem waiting in the wings.

In conclusion, amyloidosis is no longer rare. Physicians must think of amyloidosis early as differential diagnosis to initiate specific confirmatory investigations or a tissue biopsy enabling early diagnosis to allow for more effective treatments and better outcomes.

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