JACC: CARDIOONCOLOGY VOL. 2, NO. 3, 2020

EDITORIAL COMMENT

The Incremental Value of Diuretic Dose in Staging Systems for Transthyretin Cardiac Amyloid

Keep It Simple*

Martha Grogan, MD

Transthyretin (TTR)-type cardiac amyloidosis (ATTR-CM) is increasingly recognized as an important cause of heart failure (1). The acceptance of technetium-labeled nuclear scintigraphy for nonbiopsy diagnosis has revolutionized the diagnosis of this condition (2). Until recently, the only treatment options for ATTR-CM were organ transplantation or supportive care. The ATTR-ACT study (3) demonstrated that the TTR stabilizer, tafamidis, decreased mortality and heart failure hospitalizations and ushered in a new era of awareness of ATTR-CM. Prognostic staging systems for ATTR are important in patient counseling, determining treatment options, including timing of advanced therapies for heart failure or palliative care.

We proposed the Mayo Clinic cardiac biomarker staging for patients with wild-type ATTR-CM (ATTRwt) using thresholds for troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to define 3 stages of disease (4). Gilmore et al. (5) reported the UK staging system using NT-proBNP and estimated glomerular filtration rate. Both systems reported a threshold of NT-proBNP of 3,000 pg/ml. The Mayo model uses a troponin T threshold of 0.05 ng/ml, whereas the UK model uses an estimated glomerular filtration rate of <45 ml/min/1.73 m^2. The UK model included patients with both ATTRwt and hereditary ATTR-CM.

In this issue of *JACC: CardioOncology*, Cheng et al. (6) report the incremental value of diuretic dose and New York Heart Association (NYHA) functional class added to the Mayo and UK staging systems. Their study included 309 patients with ATTR-CM (66% ATTRwt) from a single center, conducted between 2002 and 2018 (Columbia University, New York). The authors reported that diuretic dose and NYHA functional class were independent predictors of mortality when added to the previously reported staging systems. The Seattle Heart Failure Model (SHFM) was able to stratify this cohort according to risk, but the 5-year predicted survival using SHFM was higher at 53.7% than the observed 36.7%. The authors noted that the "modified" Mayo and UK staging systems (adding diuretic dose and NYHA functional class) provided discriminatory results similar to the SHFM yet were easier to calculate with less input of variables.

The current study does not include echocardiographic findings in the analysis. In developing the Mayo staging system, multiple echocardiographic variables were studied, with the exception of left ventricular strain, which was not available in many in our cohort. Only reduced left ventricular ejection fraction remained independently predictive of survival in the multivariable model including cardiac biomarkers. The only echocardiographic variables reported by the UK group were interventricular septal thickness and left ventricular ejection fraction, again

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

From the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA. Dr. Grogan has reported she has no relationships relevant to the contents of this paper to disclose.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2020.07.004

JACC: CARDIOONCOLOGY, VOL. 2, NO. 3, 2020
SEPTEMBER 2020:425–7

only the latter remained significant in multivariable analysis. Cardiovascular diagnosis usually includes imaging; thus cardiologists and patients have a tendency to focus on those results. Although cardiovascular imaging has revolutionized the diagnosis of cardiac amyloidosis, the role in prognosis is less clear. When the addition of imaging variables to the staging systems is considered, the availability, reproducibility, and incremental value must also be considered.

In contrast to the current study, NYHA functional class was not independently predictive of survival in the UK staging system. The discordant results of NYHA functional class as a predictor of mortality is not discussed by the authors but may be reflective of a smaller cohort evaluated by a small number of providers with less variability. Limitations of the interobserver variation in determining the NYHA functional class may limit the use of this variable in larger cohorts.

The report by Cheng et al. (6) validates the Mayo and UK staging systems and demonstrates the incremental value of adding diuretic dose and NYHA functional class. Most clinicians incorporate a variety of factors in assessing prognosis. Ideally the staging systems are used as reference points and then tailored accordingly, using the overall clinical assessment. This study, along with the other reports cited, suggests that complex models are probably not needed for prognosis in ATTR-CM. Simple models are easily remembered and incorporated into patient visits.

We have now entered a new era of therapy for ATTR-CM. Although the original and proposed "modified" Mayo and UK staging systems provide prognostic estimates based on natural history, these models are not applicable to the majority of newly diagnosed patients who will receive therapy. Our new challenges to prognosis of ATTR-CM are 3-fold: 1) determining prognosis in treated patients; 2) assessing response to therapy; and 3) determining outcomes for patients with noncardiac TTR amyloid deposition, such as those found in carpal tunnel tissue and spinal stenosis.

Analysis of the ATTR-ACT study and ongoing cardiac trials of TTR-silencer therapy provides an opportunity to evaluate prognostic staging systems in the modern treatment era and to determine markers of therapeutic response. It is hoped that these analyses will be forthcoming, although sponsors may be reluctant to report detailed predictors of nonresponse after drug approval. Patients almost uniformly seek information regarding treatment response. As tafamidis slows the progression of disease, we do not currently have a metric to assess response. Although stabilization or only mild progression of cardiac biomarkers, diuretic dose, hospitalizations, and other simple clinical variables may be reassuring, those variables do not necessarily answer the patient's question: "Is this drug helping me?"

Due to the focus on imaging, patients often inquire about the results of follow-up studies, usually wondering if there has been regression of myocardial thickening. Given the challenges of determining prognosis using echocardiographic variables, caution is needed in enthusiasm for using these measures to assess therapeutic response. Part of the challenge lies in the pathophysiology of ATTR-CM, which is likely complex and remains incompletely understood. Dr. Rodney Falk appropriately coined the term "toxic-infiltrative cardiomyopathy" in reference to the toxicity of circulating light chains (AL) to cardiomyocytes in AL (7). Similar mechanisms of cardiomyocyte toxicity due to TTR oligomeric intermediates have been reported in ATTR (8,9). Cardiac amyloidosis is not a simple infiltrative condition, even though most cardiologists tend to think of it that way. Although intraventricular septal thickness was one of the first prognostic markers described, that variable is not independently predictive of survival in AL or ATTR. Measurements of overall cardiac function and physiologic adaptation may be more important in assessing response to therapy than simple structural variables. The time frame between the onset of noncardiac manifestations such as carpal tunnel syndrome and spinal stenosis suggests that ATTR-CM may develop very slowly which perhaps allows for physiologic adaptation of the heart, lungs, and peripheral vasculature. If treatment is successful in slowing progression or promoting regression of disease, the changes may be difficult to detect with current cardiac imaging techniques, at least in the short term.

The next frontier in determining prognosis in ATTR lies in the assessment of patients found to have TTR deposition in noncardiac tissues. Many centers are performing clinical or research studies to detect the presence of TTR in ligaments from carpal tunnel release or surgery for spinal stenosis. Although patients with ATTR-CM often have a history of carpal tunnel syndrome or spinal stenosis, it is not known if all patients with TTR amyloid in these tissues will develop ATTR-CM. These patients may be considered "Stage A" ATTR, at risk for the development of ATTR-CM, analogous to the stages of heart failure. What prognostic models could guide the appropriateness and timing of therapeutic interventions with TTR stabilizers or silencers? Are there some "Stage A" patients with ATTR deposition

in noncardiac tissues for whom we could truly prevent the development of cardiac disease? Perhaps some very early stage ATTR-CM patients may benefit from standard heart failure therapy directed at modulating systemic responses, despite the observation that those with advanced ATTR-CM usually do not tolerate those medications well. More research into the clinical course and response to therapy of ATTR-CM is needed to identify factors that will allow us to create staging models for the current era to determine prognosis, guide therapy, and change the natural history of this devastating disease.

ADDRESS FOR CORRESPONDENCE: Dr. Martha Grogan, Department of Cardiovascular Diseases, Mayo Clinic, 200 SW First Street, Rochester, Minnesota 55905. E-mail: grogan.martha@mayo.edu. Twitter: @MarthaGrogan1.

REFERENCES

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;73:2872–91.

2. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404–12.

3. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.

4. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014–20.

5. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2018;39:2799–806.

6. Cheng RK, Levy WC, Vasbinder A, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. J Am Coll CardioOnc 2020;2:414–24.

7. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016;68:1323–41.

8. Reixach N, Deechongkit S, Jiang X, Kelly JW, Buxbaum JN. Tissue damage in the amyloidoses: transthyretin monomers and nonnative oligomers are the major cytotoxic species in tissue culture. Proc Natl Acad Sci U S A 2004;101:2817–22.

9. Alhamadsheh MM, Connelly S, Cho A, et al. Potent kinetic stabilizers that prevent transthyretin-mediated cardiomyocyte proteotoxicity. Sci Transl Med 2011;3:97ra81.

KEY WORDS cardiac amyloidosis, heart failure, transthyretin