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EDITORIAL COMMENT

Evaluating Prognosis in AL Amyloidosis

Can LV Strain Play a Role?*

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If untreated, light chain (AL) cardiac amyloidosis is a rapidly progressive disease with short survival. In the 1980s, therapy with oral prednisone and melphalan (an alkylating agent) was introduced for treatment of AL amyloidosis (1). Despite a modest benefit in survival among patients with noncardiac AL amyloidosis, this therapy was not beneficial when the heart was involved. It took several months to take effect, during which time many cardiac patients died. In the 1990s, high-dose intravenous melphalan with autologous stem cell transplantation was shown to produce hematological remission in a high proportion of patients with AL amyloidosis. Remission correlated with cessation of disease progression and improvement in organ function and well-being. Unfortunately, with this highly intensive therapy, patients with cardiac involvement commonly succumbed to treatment-related mortality (2). Thus, although overall survival for AL amyloidosis improved, patients with severe cardiac disease were either excluded from stem cell transplantation or were at risk of dying from a treatment designed to prolong life.

The high mortality of untreated patients coupled with the high morbidity and/or mortality of a potentially life-prolonging therapy led to an attempt to risk stratify patients at diagnosis. With the development of left ventricular (LV) myocardial longitudinal strain imaging, studies showed that patients with amyloidosis had significant impairment in longitudinal strain, even before any changes in ejection fraction, and that abnormalities in strain could predict a better or worse prognosis (3). However, the technique was not widely used and did not find a place in pre-chemotherapy assessment for patients with cardiac amyloidosis. The development of robust biomarkers, particularly, the natriuretic peptides and troponin, offered a biochemical marker for severity of disease in AL cardiac amyloidosis, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was found to have incremental prognostic benefit when added to standard echocardiographic parameters (4). In 2004, investigators at the Mayo Clinic proposed a staging system based on biomarkers that could predict survival in newly diagnosed patients with systemic amyloidosis with or without cardiac involvement (5). The system was revised in 2012, based on new cutoff levels of troponin T and NT-proBNP and addition of a score for marked excess of either lambda- or kappa-free light chains (6). The model was developed based on a large dataset of newly diagnosed patients with AL amyloidosis and validated in 2 smaller, but robust groups of patients who underwent either stem cell transplantation or enrolled in other clinical trials. This staging system was quickly adopted by the hematological community. However, it is critical to recognize that most patients in the derivation and validation sets were treated in an era in which high-dose chemotherapy and autologous stem cell transplantation was one of the few available therapies. By

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TABLE 1 Summary of Studies That Used GLS for Risk Stratification of Patients With AL Amyloidosis

		Baseline Characteristics			Strain Analysis	Salient Results		
First Author (Ref. #)	N	Mean Age, yrs	Females (%)	LVEF (%)	Technical Details	Outcome	Independent Predictor of Events	Other Key Findings
Bellavia (8)	249 Systemic AL	63	38	62	Vivid 7, GE Vingmed Ultrasound AS, Horten; EchoPAC, GE Vingmed Ultrasound AS	ACD	Peak basal anteroseptal LS ≥−7.5%	Peak longitudinal systolic basal anteroseptal strain ≤−7.5% defined a high-risk group of patients
Koyama (3)	119 Systemic AL	58	47	LVFS, 37	Vivid Five System, Vingmed-GE; Vivid Five System, Echopac 6.3.6, GE Vingmed Ultrasound	ACD/CD	Mean LV basal strain −12% for CD and −13% for ACD	In patients with heart failure, mean LV basal strain was the only independent predictor of CD (−4.4%) and ACD (−4.6%) Strain rate and strain showed significant differences among the 3 groups (no cardiac involvement, cardiac amyloidosis without HF, cardiac amyloidosis and HF).
Buss (9)	206 Systemic AL	60	46	52	iE33, Philips Medical Systems; TomTec Imaging Systems	ACD or cardiac transplant	LS −10.65% and 2D-GLS −11.78%	LS and 2D-GLS both offered significant incremental value compared with clinical variables (age, Karnofsky index, NYHA functional class) and serological biomarkers (NT-proBNP and cTNT)
Barros-Gomes (10)	150 Systemic AL	64	35	65	Vivid E9 GE Medical System; EchoPAC PC version 6.0, GE and Syngo VVI	ACD	GLS_{GE} ≥−14.81% and GLSvvi ≥−15.02%	2D-STE predicted outcome in subjects with cardiac involvement and provided incremental prognostic information over the current prognostic staging system, which is based primarily on serum cTnT, NT-proBNP, and FLC-diff. Two methods of GLS were tested
Salinaro (11)	61 Cardiac AL	57	54	57	GE Vivid 7 echo system; GE EchoPAC	ACD	GLS ≥−10.2%	GLS predicted survival above cardiac biomarkers and detected early cardiac functional improvement following chemotherapy
Chuy (12)	94 Systemic AL Mayo stage III or IV	64	39	60	Vivid E9, GE and iE33, Philips; TomTec Imaging Systems	ACD	GLS ≥−14.2%	GLS had higher median survival and 5-yr survival rate and provided incremental value over BNP, Tn, and LVEF for predicting survival

All strain values were systolic and longitudinal.

2D-GLS = 2-dimensional global longitudinal strain; 2D-STE = 2-dimensional speckle tracking echocardiography; ACD = all cause death; AL = light chain amyloidosis; BNP = brain natriuretic peptide; CD = cardiac death; HF = heart failure; cTNT = cardiac troponin T; diff = difference; EF = ejection fraction; FLC = free light chain; FS = fractional shortening; LS = longitudinal strain; LV = left ventricular; NYHA = New York Heart Association; OS = overall survival; Tn = troponin; VVI = velocity vector imaging.

the time the revised guidelines were published, additional therapies were being used with particular success and low toxicity. As such, the number of patients treated with stem cell transplantation decreased and the overall prognosis of cardiac patients improved, potentially rendering the staging system at least inaccurate for the modern era, even as it was being published.

The limitations of the Mayo staging system among patients treated predominantly with proteasome inhibitor–based regimens were confirmed in a study of 194 patients with a new diagnosis of systemic AL amyloidosis who were seen between 2009 and 2016 (7). For patients in stage III, whose median survival in the group of patients initially published in the revised prognostic staging system was 14 months, median survival was now reported at 59 months. Patients in stage IV, those who had, by definition, significant elevations in NT-proBNP and troponin, as well as a high differential in AL levels, still had a poor median survival of 6 months. However, the investigators pointed out that only 14% of the patients in their series fell into stage IV compared with 23% in the Mayo Clinic series. This suggested that the disease was being diagnosed earlier than previously done.

The use of LV strain for prognosis in AL amyloidosis is not new. **Table 1** shows a summary of previous studies. In this issue of *JACC: CardioOncology,* Lee Chuy et al. (12) sought to determine whether LV global longitudinal strain could add to the prognostic ability of the Mayo staging system in more seriously ill patients, namely, those in stages III and IV. They studied 94 patients, of whom 38 had stage IV disease. Survival data were shown for the 88 patients who had adequate strain values. Global strain equal to or more negative than −14.2% best discriminated between patients with better or poorer survival, and the investigators concluded that baseline global

longitudinal strain was an independent predictor of overall survival beyond the Mayo staging system. Although we agree that the analysis showed an additive benefit of measuring global longitudinal strain in these 88 patients, we believe that a careful analysis of why this might be argues for great caution in extrapolating these findings to clinical practice. The median survival for patients in stage III was only 15 months, similar to the older Mayo survival cohort and much different from the 59-month median survival found with current therapy. The study included 26% of patients who underwent stem cell transplantation (an unusually high percentage for patients with significant AL cardiac amyloidosis treated in the modern era), and another 20 patients whose initial treatment was melphalan and dexamethasone. This therapy is rarely used now because of the superior efficacy of proteasome inhibitor–based regimens and regimens that incorporate daratumumab (an antibody directed against CD38, which is overexpressed in plasma cell dyscrasias) (13). Thus, the patients studied did not appear to be a group that underwent typical modern day therapy. The overall group from which the conclusions were derived was relatively small, and there was no validation group, which is a most important aspect of any study attempting to define a novel prognostic index. Generally, patients with advanced cardiac amyloidosis have severe impairment of global longitudinal strain. The finding of a global strain of at least −14.2% in one-quarter of the patients classified as Mayo stage IV suggested that their cardiac biomarkers might have been marginally higher than the cutoff, rather than the more common finding of markedly elevated biomarkers.

It is worthwhile considering the reason why global longitudinal strain might have been such a relatively potent prognostic indicator in this study. The Mayo staging system consists of 2 cardiac biomarkers (troponin, and NT-proBNP or BNP) and 1 hematological marker. Significant amyloid cardiac disease is usually associated with considerable elevation in both NT-proBNP and troponin. Patients with more than mild elevation of only 1 of these 2 biomarkers tend to be less sick than those with elevation of both. The investigators' Table 1 showed that 74 of the 94 patients had a free light chain difference of ≥18 mg/dl. By definition, because all 38 patients in Mayo stage IV had to have elevation in all 3 biomarkers, this left 36 patients among the 56 patients in Mayo stage III (64%) who met the criteria for marked free light chain elevation, and thus, who had to have elevation in only 1 of the 2 cardiac biomarkers. Because those with an elevation in only 1 cardiac biomarker tended to be a somewhat heterogenous group of patients, it was not surprising that some would have relatively well-preserved LV longitudinal strain, whereas others had a greater impairment. The latter group had a worse prognosis. It would have been interesting for the investigators to explore the incremental benefit of longitudinal strain in the one-third of patients in Mayo class III who were so classified because of significant abnormalities in both BNP and troponin and to have compared them with those who had 1 of those biomarkers that crossed the classification point.

The investigators suggested that their findings "may have important clinical implications for the development and evaluation of treatment strategies targeted towards specific patient groups and may improve risk classification to help refine optimal selection of patients for risk adapted therapeutic approaches." Although we agree that, in the future, incorporation of advanced measurements of ventricular function using strain imaging may be helpful, we feel their conclusions are based on a series of patients with a relatively low overall median survival compared with other published data and without validation among patients treated with current antiplasma cell therapy. In a therapeutic field for AL cardiac amyloidosis that is growing rapidly, prognostic indexes can be outdated by the time they are published because they rely on therapy that is no longer first-line. We look forward to the research advances to come in the modern treatment era.

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