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EDITORIAL COMMENT

Raise the Flag

Is Low QRS Voltage Ready to Advance to a Prognostic Factor?*

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We advance by the harmonious assembling of facts by many observers.
—Charles H. Mayo, MD

Timely diagnosis of cardiac amyloidosis (CA) alongside prompt initiation of disease-targeted therapy remains a challenge. In general, disease awareness is increasing and there is growing recognition of CA in patients with heart failure with preserved ejection fraction (13%-17%) and aortic stenosis (16%).[1] However because of the masquerading nature of amyloidosis, initial symptoms, time to recognition, and therapy initiation remain problematic. Patients will often wait more than a year to receive a diagnosis, despite seeing multiple providers.[1-3] Fortunately, advancements in screening and therapy provide hope for our patients.[4] Treatment options are now available for patients with transthyretin (ATTR) amyloidosis (silencers and stabilizers), and combination cytotoxic and immunotherapies have greatly improved the treatment and outcomes in light chain (AL) amyloidosis (ie, ANDROMEDA [A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination With Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light-Chain (AL) Amyloidosis]).[4,5] However, current staging systems are not reflective of these advancements. Prior to therapeutic innovations with disease-targeted therapeutics and ANDROMEDA,[5] the expected median survival for wild-type and hereditary ATTR amyloidosis was 3.5 and 2.5 years, respectively,[6] and expected median survival for AL amyloidosis was 60% at 2 years.[7,8] These therapies are changing the natural course of amyloidosis, and time will tell what the future holds for our patients.

Electrocardiographic (ECG) findings are known to be associated with CA, and findings such as low or decreased voltage, "pseudoinfarct" pattern, and atrioventricular conduction disease might suggest underlying CA. Prior studies, albeit with differing criteria for low QRS voltage (LQRSV), have consistently shown that LQRSV in CA has a prognostic impact.[9-11] A "red flag" should be raised, and CA considered, when there is discordance between ECG voltage and ventricular wall thickness on imaging.[4]

Although the search for the meaning of discordant LQRSV in CA is not novel, the journey is far from complete. Is LQRSV a marker for mortality? In this issue of *JACC: CardioOncology*, Cipriani et al[12] report on a large, retrospective, multicenter study focusing on LQRSV in CA, assessing its prevalence, identifying possible clinical and echocardiographic relationships, and investigating its prognostic impact.

The investigators found an overall prevalence of LQRSV of 41% (55% in AL CA and 35% in ATTR CA). This is slightly lower but similar to prior studies (60% in AL CA and 25%-40% in ATTR CA).[13] They also show that LQRSV is significantly associated with markers of advanced disease. Although younger age was noted in patients with AL CA, this is likely reflective of the known epidemiology compared with wild-type ATTR. In the risk models presented, LQRSV helped discriminate survival at 40 months for both AL (90% vs 60%) and ATTR (95% vs 80%) CA. The investigators also show that the presence of LQRSV was associated

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with increased cardiovascular mortality in both AL and ATTR CA.[12]

Those with ATTR CA and LQRSV were less likely to have early disease, as defined by National Amyloidosis Centre (NAC) stage 1.[12,14] Additionally, LQRSV seemed to have discriminative ability in patients with intermediate NAC staging or NAC stage 2. Mussinelli et al[10] previously showed that the presence of LQRSV in AL CA was able to differentiate Mayo stage II patients' survival (historic Mayo staging system), with no effect in patients with stage I or III disease. They reported worse survival at 6 months (85% vs 92%) and 1 year (88% vs 75%) in stage II patients with LQRSV.[10] How do we explain this? Their study, like prior studies, suggest a "Goldilocks-type phenomenon": LQRSV does appear to be a marker of more advanced disease, but it is most useful at the intermediate stage, before pathology becomes too advanced. LQRSV may serve as a future marker to intensify therapy and should further support the idea to "raise a flag" and query if this could be CA.

Cipriani et al[12] confirm the presence of LQRSV as a marker of increased morbidity and mortality. However, additional population-based, prospective studies are needed to firmly establish LQRSV as an independent prognostic factor in both AL and ATTR CA. Interpretation remains limited, as staging criteria was not applied to patients with AL CA because of a lack of cardiac biomarker data availability, and only the NAC staging system was evaluated in this observational cohort. A larger patient sample size and the inclusion of patients with more advanced CA are needed to power future prospective studies. The majority of patients in this study were classified as having only mild to moderate cardiac disease by New York Heart Association functional classification and NAC staging. Survival analysis was also calculated with day 1 being the first day of evaluation and ECG recording at the referral center, rather than the day of diagnosis, to avoid any time referral bias. We are thus unable to draw conclusions regarding the temporal associations of these ECG findings (eg, time from symptom onset to diagnosis and manifestation of LQRSV on electrocardiography) and whether treatment prior to being evaluated at a referral center affected the data analysis. Confirmatory studies should be performed prior to full generalization of these results. The guideline standard for the low-pass filter setting in adults of 150 Hz was present in 91% of study subjects. The investigators do not comment on what occurred in the other 9% of patients. For a study focused on ECG findings, more rigorous standardization of ECG machines would be ideal.

In summary, Cipriani et al[12] continue to advance the field by adding to our understanding of the relationship between LQRSV and CA and its association with increased mortality and morbidity. Is electrocardiography ready to graduate from "red flag" to having an incremental prognostic impact on patient comes? More investigation is needed to understand the relationship between LQRSV and current AL and ATTR staging systems to determine this. Artificial intelligence and electrocardiography are likely to become a routine part of our practice as both screening and prognostic tools[2,15]; there is hope that in the future it can be used to predict response to therapy and guide decision making. This is a promising start, with more observations to come as the field and practice continue to evolve.

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Dr Fonseca is a consultant for AbbVie, Amgen, Bayer, Bristol Myers Squibb/Celgene, GlaxoSmithKline, H3 Therapeutics, Janssen, Juno, Karyopharm, Kite, Merck, Novartis, Oncopeptides, OncoTracker, Pfizer, Pharmacyclics, Regeneron, Sanofi, and Takeda; and is a scientific advisory board member for Adaptive Biotechnologies, Caris Life Sciences, OncoMyx, and OncoTracker. Dr Rosenthal is a scientific advisory board member for Pfizer and Alnylam; and has received research (clinical trial) grant support from Akcea. Dr Fatunde has reported that he has no relationships relevant to the contents of this paper to disclose.

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