JACC: HEART FAILURE VOL. 10, NO. 2, 2022

PUBLISHED BY ELSEVIER

CLINICAL RESEARCH

Transthyretin V142I Genetic Variant and Cardiac Remodeling, Injury, and Heart Failure Risk in Black Adults

Amanda C. Coniglio, MD,[a,*] Matthew W. Segar, MD, MS,[b,*] Rahul S. Loungani, MD,[a] Jainy J. Savla, MD,[c] Justin L. Grodin, MD, MPH,[b] Ervin R. Fox, MD,[d] Sonia Garg, MD,[a] James A. de Lemos, MD,[b] Jarett D. Berry, MD, MS,[b] Mark H. Drazner, MD, MSc,[b] Sanjiv Shah, MD,[e] Michael E. Hall, MD,[d] Amil Shah, MD,[f] Sadiya S. Khan, MD, MSc,[g] Robert J. Mentz, MD,[a] Ambarish Pandey, MD, MSCS[b]

ABSTRACT

OBJECTIVES This study evaluated the association of transthyretin (TTR) gene variant, in which isoleucine substitutes for valine at position 122 (V142I), with cardiac structure, function, and heart failure (HF) risk among middle-aged Black adults.

BACKGROUND The valine-to-isoleucine substitution in the TTR protein is prevalent in Black individuals and causes cardiac amyloidosis.

METHODS Jackson Heart Study participants without HF at baseline who had available data on the TTR V142I variant were included. The association of the TTR V142I variant with baseline echocardiographic parameters and repeated measures of high-sensitivity cardiac troponin-I (hs-cTnI) was assessed using adjusted linear regression models and linear mixed models, respectively. Adjusted Cox models, restricted mean survival time analysis, and Anderson-Gill models were constructed to determine the association of TTR V142I variant with the risk of incident HF, survival free of HF, and total HF hospitalizations.

RESULTS A total of 119 of 2,960 participants (4%) were heterozygous carriers of the TTR V142I variant. The TTR V142I variant was not associated with measures of cardiac parameters at baseline but was associated with a greater increase in high-sensitivity troponin I (hs-TnI) levels over time. In adjusted Cox models, TTR V142I variant carriers had significantly higher risk of incident HF (HR: 1.80; 95% CI: 1.07-3.05; $P = 0.03$), lower survival free of HF (mean difference: 4.0 year; 95% CI: 0.6-6.2 years); $P = 0.02$), and higher risk of overall HF hospitalizations (HR: 2.12; 95% CI: 1.23-3.63; $P = 0.007$).

CONCLUSIONS The TTR V142I variant in middle-aged Black adults is not associated with adverse cardiac remodeling but was associated with a significantly higher burden of chronic myocardial injury, and greater risk of incident HF and overall HF hospitalizations. (J Am Coll Cardiol HF 2022;10:129–138) © 2022 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA; [b]Department of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas, USA;[c]Division of Cardiology, Department of Internal Medicine, University of Washington School of Medicine, Seattle, Washington, USA; [d]Department of Internal Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA; [e]Division of Cardiology, Department of Internal Medicine, Northwestern University School of Medicine, Chicago, Illinois, USA; [f]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; and the [g]Division of Cardiovascular Medicine, Department of Internal Medicine, Northwestern University School of Medicine, Chicago, Illinois, USA. *Drs Coniglio and Segar contributed equally to this work.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 13, 2021; accepted September 7, 2021.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2021.09.006

ABBREVIATIONS AND ACRONYMS

BNP = brain natriuretic peptide

CMR = cardiac magnetic resonance

CV = cardiovascular

HF = heart failure

LV = left ventricle

LVH = left ventricle hypertrophy

TTR = transthyretin

Heart failure (HF) affects Black individuals at higher rates and is associated with worse outcomes than other race/ethnic groups (1). Cardiac amyloidosis in Black individuals is commonly associated with the autosomal dominant transthyretin (*TTR*) gene variant, in which isoleucine substitutes for valine at position 122 (TTR V142I [p.V142I, rs76992529]) (2). Prior observations from multiethnic cohorts have demonstrated an increased risk of HF among self-reported older Black adults carrying the V142I variant in the *TTR* gene (3,4). However, the association of the TTR V142I variant with the overall HF hospitalization burden (incident plus recurrent) has not been evaluated. Furthermore, survival free of HF among individuals with vs without the TTR V1421I variant and the association of TTR V142I variant carrier status with cardiac structure and function have not been previously characterized in a middle-aged (21-65 years of age) community-dwelling cohort of exclusively Black individuals. This is particularly relevant considering that clinical penetrance of the TTR V142I variant increases with older age and thus would have implications for screening at a younger age (2). Accordingly, we evaluated the association of TTR V142I variant carriers status with cardiac structure, function, and risk of adverse cardiovascular (CV) events, including incident and recurrent HF events, among Black participants of the Jackson Heart Study (JHS).

SEE PAGE 139

METHODS

STUDY POPULATION. We used participant-level data from the JHS for the present analysis. The study design, recruitment, and baseline assessments in the JHS have been previously described (5,6). Briefly, JHS was a prospective study of 5,306 self-identified Black adults aged >21 years of age living in Jackson, Mississippi and the surrounding metropolitan area. Three visits were conducted between 2000 and 2012. For this analysis, examination 1 (2000-2004) was considered the baseline. The present investigation was limited to the JHS cohort participants who had available data for the V142I genotype (n = 3,447). We excluded participants from the study with prevalent HF as identified by self-report at the baseline visit (n = 346). Furthermore, because the adjudication of incident HF events did not start until 2005, we further excluded participants who had self-reported HF before 2005 (n = 141, including 2 TTR V142I carriers and 139 noncarriers) (Supplemental Figure 1). The final analysis cohort included 2,960 participants. All participants in the JHS provided informed and written consent, and the coordinating center institutional review boards approved study protocols.

CLINICAL COVARIATES. Participants underwent comprehensive examinations at baseline and at each study visit using standardized protocols (5,6). Demographic covariates and medical history were obtained by self-reported questionnaires. Blood pressure measurements were obtained as the average of 2 blood pressure readings using a random-0 sphygmomanometer. Body mass index was calculated as kg/m^2. The presence of diabetes was defined as a history of diabetes, fasting blood glucose ≥126 mg/dL, or use of diabetes mellitus medications. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Laboratory measurements were obtained in participants after >12 hours of fasting and assessed using standard laboratory techniques. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation (7).

CARDIAC STRUCTURE, FUNCTION, AND BIOMARKER ASSESSMENT. Echocardiographic examinations (Sonos-4500; Phillips Medical Systems) were performed at visit 1 by trained sonographers and interpreted at a centralized reading center as reported previously and detailed in the Supplemental Methods (5,8). Left ventricular end-diastolic volume was estimated by the Tehicholz formula (9). High-sensitivity troponin-I (hs-TnI) (ARCHITECT, Abbott Diagnostics) and brain natriuretic peptide (BNP) levels (Siemens Advia Centaur) were also measured using the serum/plasma samples collected at visit 1 (for BNP) and visit 1, 2, 3 (for hs-cTnI) as previously reported (10,11). Cardiac magnetic resonance (CMR) imaging (1.5-T system, Siemens Espree) parameters was obtained in a subset of participants and began towards the end of visit 2 and continued through visit 3 (2008-2012) using a previously described protocol and detailed in the Supplemental Methods (12). Left ventricular hypertrophy (LVH) on ECG was defined using Sokolov-Lyon criteria (sum of lead V_1 S-wave amplitude plus maximum V_5 to V_6 R-wave amplitude ≥35 mm) and Cornell voltage criteria (sum of lead aVL R-wave amplitude plus lead V_3 S-wave >28 mm in men and >22 mm in women). Because cardiac amyloid infiltration is associated with increased LV mass disproportionate to ECG voltage, the LV mass index-to-QRS voltage ratio was also assessed as previously described (13). The QRS voltage was measured as the sum of the absolute value of the QRS complex amplitude in leads I, II, III, aVL, aVF, and aVR. Myocardial contraction

fraction was defined as the ratio of LV stroke volume-to- myocardial volume (14). Myocardial volume was estimated by the LV myocardial mass, estimated by American Society of Echocardiography formula, divided by myocardial tissue density (1.04 g/mL) (15). Malignant LVH was defined as LVH on ECG plus evidence of myocardial injury (high-sensitivity cardiac troponin-I [hs-cTnI] ≥4 ng/L for females and hs-cTnI ≥6 ng/L for males) (11,16).

V142I PATHOGENIC VARIANT GENOTYPING. Genetic samples were obtained from consented participants, and the DNA samples were genotyped using Affymetrix Genome-Wide Human single-nucleotide variation (SNV) (formerly SNP) array 6.0 at the Broad Institute of Harvard and Massachusetts Institute of Technology (17). Individuals with available genetic data for the *TTR* gene and associated V142I genetic variant (p.V142I, rs76992529) were included in the present analysis (18). As reported previously, the V142I variant results from a G-to-A transition at the CG dinucleotide codon of amino acid 122 of a mature TTR protein. Of the 3,447 JHS participants who were genotyped, a total of 127 were heterozygous carriers (minor allele [A]) for the TTR V142I variant. There were no participants with the homozygous TTR V142I variant.

CLINICAL OUTCOMES. Primary outcomes of interest were incident and recurrent HF hospitalization events. Secondary outcomes of interest were all-cause mortality and nonfatal atherosclerotic cardiovascular disease event (atherosclerotic cardiovascular disease, a composite of stroke or nonfatal myocardial infarction). Outcome events were formally adjudicated beginning in January 2005 based on annual telephone interviews, hospital discharge lists, and hospitalization data review as reported previously (11,19). Diagnoses were reviewed and adjudicated by trained medical personnel and based on International Classification of Diseases, ninth revision codes. Outcomes were adjudicated up to 2016. Prior to 2005, events were obtained by self-reported hospitalizations. Time to event was recorded from January 1, 2005, to either the date of incident HF hospitalization or December 31, 2016.

STATISTICAL ANALYSIS. The study population was stratified based on the TTR V142I variant carrier status. The baseline demographic and clinical characteristics and cardiac structure and function (by echocardiogram at visit 1 and CMR at visit 3), and levels of cardiac biomarkers (visit 1) were compared between TTR V142I variant carriers vs noncarriers using one-way ANOVA for continuous and chi-squared test for categorical variables. The baseline characteristics were also compared among those who did vs did not develop incident HF on follow-up within each group. The association between TTR V142I variant carrier status and cardiac structure and function measures and biomarkers were assessed using multivariate linear regression analysis with the following adjustments: model 1 consisted of age and sex; model 2 consisted of model 1 plus SBP, body mass index (BMI), eGFR, diabetes status, and hs-cTnI. The association between TTR V142I variant carrier status and longitudinal changes in hs-TnI and ECG parameters (PR duration, QRS duration, and Cornell voltage) were assessed using linear mixed effect models for repeated measures with adjustments for the following covariates: age, sex, SBP, BMI, eGFR, diabetes status, and hs-cTn and incident HF as a time-varying covariate. Multivariate adjusted Cox models were constructed to determine the association of TTR V142I variant carriers (vs noncarriers) and the risk of incident HF, an atherosclerotic cardiovascular disease event, and all-cause mortality. Separate models were constructed for each outcome with the same model 1 and 2 adjustments described above. Differences in HF-free survival between participants with vs without the TTR V142I variant were determined using restricted mean survival time (RMST) (20). RMST is analogous to the area under the survival curve and, in this analysis, represents the mean event-free survival from baseline to incident HF. Age-specific event rates were determined using age at visit 1 and at the time of the incident HF event. Anderson-Gill models were constructed to assess the association between the presence of TTR V142I variant and risk of all hospitalizations for HF, including recurrent events in those with more than 1 event. Similarly, Anderson-Gill models were used to assess the association between TTR V142I and the recurrent HF hospitalization among individuals with an incident HF event.

Sensitivity analyses were also performed using a propensity-matched case-control approach. Participants with vs without TTR V142I variant were matched in a 1:3 ratio on age, sex, BMI, SBP, eGFR, diabetes status, and hs-cTn. Differences in baseline characteristics (clinical, ECG, biomarkers), follow-up cardiac CMR parameters, and risk of adverse CV events between the matched groups were compared using statistical tests detailed above for the primary analysis. Analyses were performed using R version 3.6.3 software (R Foundation) and considered significant with a 2-sided P value of <0.05.

RESULTS

In the present study cohort, 119 of 2,960 participants (4%) were heterozygous carriers of the TTR

TABLE 1 Baseline Characteristics Stratified by TTR V142I Variant Carrier Status

	TTR V142I Variant Carriers (n = 119 [4%])	TTR V142I Variant Non-Carriers (n = 2,841 [96%])	*P* Value
Clinical, laboratory, and ECG characteristics (visit 1, dates 2000-2004)			
Age, y	53.9 ± 11.8	54.9 ± 12.7	0.4
Men	36 (30.3)	1,071 (37.7)	0.12
Prior tobacco Use	36 (30.3)	933 (32.9)	0.61
Systolic blood pressure, mm Hg	126 ± 15	127 ± 17	0.55
BMI, kg/m^2	31.4 ± 7.5	31.8 ± 7.2	0.56
Hypertension	59 (49.6)	1,579 (55.6)	0.23
Diabetes	18 (15.1)	655 (23.1)	0.06
Chronic kidney disease	3 (2.5)	135 (4.8)	0.36
eGFR, mL/min/1.73m^2	86.8 ± 17.6	87.6 ± 15.6	0.656
HbA1c, %	5.9 ± 1.1	6.0 ± 1.3	0.3
Troponin, ng/L	6.2 ± 11.3	6.1 ± 16.7	0.92
BNP, pg/mL	16.9 ± 29.9	14.7 ± 23.7	0.32
PR duration, ms	172.1 ± 28.1	171.7 ± 31.2	0.88
Aggregate QRS amplitude from limb leads, mV	18.2 ± 8.0	18.0 ± 8.0	0.81
Cornell voltage, microV	1,551.9 ± 653.4	1,488.4 ± 640.2	0.29
LVH by Sokolow-Lyon	4 (5.3)	119 (6.5)	0.86
LVH by Cornell voltage	4 (3.4)	54 (1.9)	0.43
Malignant LVH	0.0 (0.1)	0.0 (0.2)	0.56
Echocardiographic parameters (visit 1, dates 2000-2004)			
Number of participants	116 (4.1)	3,194 (95.9)	
Ejection fraction, %	62.8 ± 7.4	62.2 ± 6.9	0.34
LV mass indexed to BSA, g/m^2	71.9 ± 16.7	74.1 ± 16.8	0.26
Relative wall thickness	0.4 ± 0.1	0.4 ± 0.1	0.88
LA diameter, mm	17.8 ± 2.0	18.0 ± 2.2	0.48
E/A ratio	1.1 ± 0.3	1.1 ± 0.4	0.91
TR peak velocity, cm/s	23.6 ± 8.6	22.7 ± 7.2	0.31
Myocardial contraction fraction, %	59.3 ± 12.7	59.2 ± 11.4	0.95
LV mass index/QRS amplitude	4.7 ± 2.0	4.9 ± 2.1	0.57
CMR imaging parameters (visit 2/3, dates 2008-2012)[a]			
Number of participants, %	38 (4.3)	802 (95.7)	
Age at visit 3, y	60.4 ± 10.7	60.2 ± 10.4	0.93
LV mass indexed to BSA, g/m^2	68.1 ± 20.5	67.9 ± 16.4	0.94
LV mass indexed to allometric height, g/m$^{2.7}$	32.3 ± 10.2	32.4 ± 8.1	0.89
LV mass indexed to BSA/QRS amplitude	4.6 ± 1.9	4.4 ± 1.8	0.67
End-diastolic volume indexed to BSA, mL/m^2	59.0 ± 14.3	61.8 ± 15.1	0.28
Concentricity, (g/mL)	3.2 ± 1.1	3.0 ± 1.2	0.54
Pulse wave velocity, m/s	9.7 ± 3.8	12.8 ± 11.2	0.51
Peak systolic global circumferential strain, %	−16.0 ± 2.6	−15.5 ± 2.4	0.22

Values are mean ± SD or n (%). QRS amplitude is the sum of absolute values of the QRS amplitudes in leads I, II, III, aVL, aVR, and aVF. [a]In a subset of 840 participants who underwent CMR imaging at visit 2 (5 y from baseline) or 3 (8 y from baseline) and excluding participants with a HF event prior to visit 3.

BMI = body mass index; BNP = brain natriuretic peptide; BSA = body surface area; CMR = cardiac magnetic resonance; E/A = ratio of peak velocity blood in early diastole (left ventricular relaxation) to peak velocity blood in late diastole (atrial contraction); ECG = electrocardiography; HbA1c = hemoglobin A1c; LA = left atrium; LV = left ventricle; LVH = left ventricular hypertrophy; TR = tricuspid regurgitation; TTR = transthyretin

V142I variant. The baseline clinical, laboratory, and ECG characteristics of participants stratified by TTR V142I variant carrier status are shown in Table 1. There were no significant differences in baseline age, the proportion of women participants, and the burden of traditional CV risk factors among TTR V142I variant carriers vs noncarriers. Similarly, the echocardiographic parameters at baseline were also not different between the 2 groups. Among participants with a CMR at visit 3 (n = 840, including 38 carriers and 802 noncarriers), we observed no significant differences in LV mass, end-diastolic volume, or strain between TTR V142I variant carriers vs noncarriers. A similar pattern of results was observed for differences in baseline clinical and echocardiographic characteristics and follow-up CMR parameters in the propensity-matched case-control comparisons

between participants with vs without TTR V142I variant (Supplemental Table 1).

ADJUSTED ASSOCIATION OF TTR V142I VARIANT WITH CARDIAC STRUCTURE AND FUNCTION. We observed no significant associations between TTR V142I variant carrier status and BNP levels at baseline in the most adjusted model (Model 2) (Table 2). Similarly, we observed no significant associations between the presence of TTR V142I variant and hs-cTnI levels at baseline in the most adjusted model (Model 2) (Table 2). Finally, the presence of the TTR V142I variant was also not associated with ECG measures of cardiac structure and function at baseline, including LV ejection fraction, LV diastolic dimension, LV mass index, and relative wall thickness (Table 2).

ASSOCIATION OF TTR V142I VARIANT WITH TRAJECTORIES IN TROPONIN AND ECG PARAMETERS. A total of 2,017 participants had a baseline and at least 1 follow-up measurement of hs-TnI prior to the development of HF; 1,323 participants (65.6%) had 3 measurements of hs-TnI recorded. We observed a significant increase in hs-TnI from visit 1 to visit 3 among V142I TTR carriers (visit 1: 5.8 ng/L; visit 3: 16.0 ng/L; $P = 0.02$) but not among noncarriers (visit 1: 5.6 ng/L; visit 3: 6.1 ng/L; $P = 0.39$) (Figure 1). In adjusted linear mixed models, TTR V142I variant carrier status was significantly associated with higher levels of hs-TnI on follow-up after adjusting for other confounders (TTR + slope: 5.64 (95% CI: 1.48-9.80), TTR- slope: 0.43 (95% CI: −0.08-0.95); overall $P <$ 0.001) (Table 3). TTR V142I variant carriers who had consistently elevated hs-TnI levels on follow-up were older and had a higher burden of traditional CV risk factors than those without persistently elevated hs-TnI levels (Supplemental Table 2).

Among ECG parameters, a consistent decline in QRS duration was observed in both TTR V142I variant carriers and noncarriers, with no significant differences observed between carrier statuses. Similarly, no significant differences in Cornell voltage or PR duration trajectories were observed between TTR V142I variant carriers vs noncarriers (Table 3).

ASSOCIATION OF TTR V142I VARIANT WITH THE RISK OF HEART FAILURE AND OTHER EVENTS. Over a median follow-up of 12.0 years (IQR: 10.6-12.0 years) from 2005, we observed 258 (8.7%) incident HF events. Among TTR V142I variant carriers, 11.8% (n = 14) had incident HF on follow-up. The rate of total HF hospitalization events (incident + recurrent) among TTR V142I variant carriers was 49.6 per 1000 person-years. Among individuals without the TTR V142I variant, 8.6% (n = 244) had incident HF on follow-up, and the rate of total HF hospitalization was 31.8 per 1000 person-years. In adjusted Cox models, TTR V142I variant carrier status was significantly associated with higher risk of incident HF (HR: 1.80; 95% CI: 1.07-3.05; p = 0.03) (Table 4, model 2) and overall HF hospitalization (HR: 2.12; 95% CI: 1.23-3.63; $P = 0.007$) (Table 4, model 2, Figure 2A). Among individuals with an incident HF event, TTR V142I variant carriers had a significantly higher risk of recurrent HF hospitalization events (HR: 2.24; 95% CI: 1.22-4.12; $P = 0.009$). In RMST analysis, participants aged 40, the estimated survival free from HF was 41 years for individuals with TTR V142I variant and 45 years among those without the TTR V142I variant (mean difference: 4.0 years; 95% CI: 0.6-6.2 years; $P = 0.02$) (Figure 2B). Similar results were observed for individuals aged 60 with a mean difference of 3.8 years (95% CI for difference: 1.0-6.6 years; $P = 0.007$). There were no significant differences in the risk of all-cause mortality and atherosclerotic adverse events (a stroke or nonfatal myocardial infarction) among TTR V142I variant carriers vs noncarriers in unadjusted as well as adjusted analyses (Table 4).

A similar pattern of associations between TTR V142I variant and risk of incident HF, overall HF hospitalization, recurrent HF hospitalizations, and atherosclerotic adverse events were observed in the matched case-control analysis (Supplemental Table 3).

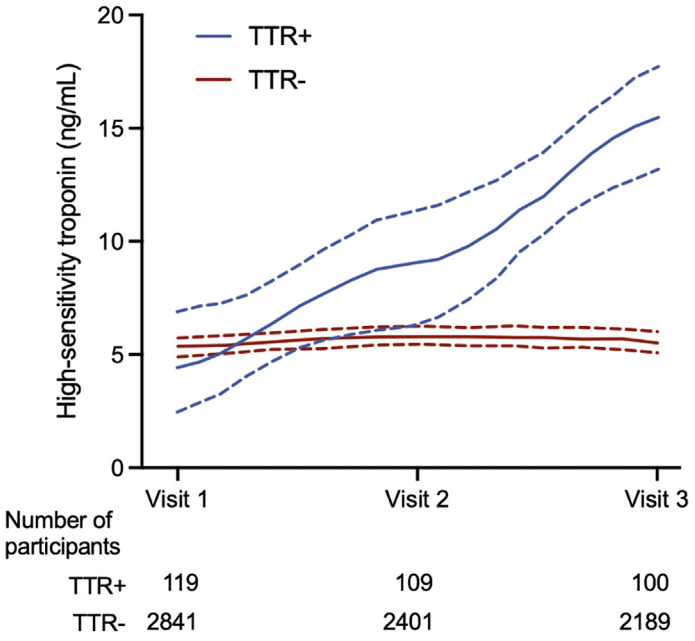
TABLE 2 Multivariate-Adjusted Associations Between V142I Pathogenic Variant and Cardiac Imaging Parameters and Biomarkers

	Model 1		Model 2	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Echocardiographic outcomes (baseline visit 1)				
Ejection fraction, %	0.52 (−0.74 to 1.79)	0.42	0.62 (−0.65 to 1.89)	0.34
Myocardial contraction fraction	−0.48 (−3.04 to 2.07)	0.71	−1.01 (−3.49 to 1.46)	0.42
RWT	−0.01 (−0.12 to 0.14)	0.88	0.03 (−0.10 to 0.16)	0.62
LV diastolic dimension to mm	0.05 (−0.74 to 0.84)	0.90	0.17 (−0.60 to 0.95)	0.67
LV mass index/QRS	0.15 (−0.30 to 0.60)	0.52	0.15 (−0.29 to 0.60)	0.50
CMR outcomes (visit 2/3)				
LV mass index	1.84 (−2.82 to 6.49)	0.44	2.01 (−2.39 to 6.41)	0.37
LV mass index/QRS amplitude	0.18 (−0.39 to 0.76)	0.53	0.21 (−0.36 to 0.78)	0.48
End-diastolic volume index	−3.07 (−9.44 to 3.30)	0.34	−2.58 (−8.88 to 3.73)	0.42
Concentricity	0.15 (−0.24 to 0.53)	0.46	0.19 (−0.20 to 0.57)	0.34
Pulse wave velocity to m/s	−3.21 (−12.44 to 6.92)	0.49	−2.93 (−12.77 to 6.92)	0.55
Mean systolic global circumferential strain	−0.40 (−1.18 to 0.37)	0.31	−0.26 (−1.02 to 0.50)	0.51
Biomarker outcomes (baseline visit 1)				
hs-cTnI[a]	0.01 (−0.13 to 0.14)	0.93	0.00 (−0.09 to 0.10)	0.93
BNP[a]	0.05 (−0.14 to 0.24)	0.59	0.04 (−0.14 to 0.23)	0.65

QRS amplitude is the sum of absolute value of the QRS amplitude in leads I, II, III, aVL, aVR, and aVF. Models were assessed by linear regression. Model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, systolic blood pressure, body mass index, estimated glomerular filtration rate, diabetes status, and high-sensitivity cardiac troponin. [a]Log-transformed.

BNP = brain natriuretic peptide; CMR = cardiac magnetic resonance; hs-cTnI = high-sensitivity cardiac troponin-I; LV = left ventricle; RWT = relative wall thickness.

FIGURE 1 Chronic Myocardial Injury Burden Over Time Among TTR V142I Carriers Versus Noncarriers



Trajectory of burden of chronic myocardial injury as assessed by circulating levels of hs-TnI on follow-up among V142I carriers vs noncarriers. Linear mixed effects models were adjusted for age, sex, systolic blood pressure, body mass index, estimated glomerular filtration rate, diabetes status, and incident HF as a time-dependent covariate. hs-TnI = high-sensitivity troponin-I.

CHARACTERISTICS OF TTR V142I VARIANT CARRIERS AND NONCARRIERS WITH VERSUS WITHOUT HF. Baseline echocardiographic characteristics of participants with vs without HF on follow-up stratified by their TTR V142I variant carrier status are shown in Table 5. Across both TTR V142I variant groups (carriers and noncarriers), individuals with (vs without) incident HF on follow-up had higher LV mass, larger left atrial size, higher relative wall thickness, and higher levels of BNP and hs-TnI at baseline. Among participants who developed HF on follow-up, there were no meaningful differences in the baseline characteristics between the TTR V142I variant carriers vs noncarriers.

DISCUSSION

In this study of community-dwelling Black individuals from the JHS cohort, the prevalence of the TTR V142I pathogenic variant was 4%. This was comparable to the prevalence of V142I carriers reported in other cohorts (2-4). We did not observe any differences in clinical characteristics, cardiac structure, function, and levels of biomarkers of myocardial injury or stress among carriers vs noncarriers in the JHS. In contrast, prior studies from the ARIC (Atherosclerotic Risk In Communities) and CHS (Cardiovascular Health Study) cohorts have demonstrated subtle abnormalities in cardiac structure, function, and natriuretic peptide levels among carriers vs noncarriers (2,4). This may be related to the older age of participants in the ARIC (aged 67-90 years) and CHS (aged 65-93 years) cohorts at the time of echocardiographic examination. These observations are consistent with the notion of delayed clinical penetrance of the V142I pathogenic variant in younger aged participants (<60 years).

We observed a significantly higher incidence of HF and higher rates of overall and recurrent HF hospitalizations among TTR V142I variant carriers (Central Illustration). Although prior observations from the ARIC and CHS cohorts have also reported a higher incidence of HF among carriers, the survival free of HF and the overall burden of HF have not been assessed previously (2,4). Our study adds to the existing published reports by demonstrating a lower survival free of HF and a greater overall burden of HF hospitalizations among middle-aged individuals of the self-reported Black race with TTR V142I variant. At age 40, the estimated survival free from HF was 4 years lower for individuals with vs without TTR V142I variant. We did not observe an increased risk of mortality among carriers (vs noncarriers), which has

TABLE 3 Slopes of Linear Mixed Effect Models of Troponin and Electrocardiographic Parameters Over Time by TTR V142I Variant Carrier Status

Outcome	TTR V142I Variant Carrier Slope (95% CI)	*P* Value	TTR V142I Variant Noncarrier Slope (95% CI)	*P* Value	Overall *P* Value[a]
hs-cTnI, ng/L	5.64 (1.48 to 9.80)	0.008	0.43 (−0.08 to 0.95)	0.10	<0.001
PR duration, ms	−2.06 (−6.06 to 1.93)	0.31	−0.41 (−1.35 to 0.53)	0.40	0.20
QRS duration, ms	−1.98 (−3.98 to 0.02)	0.05	−2.26 (−2.69 to −1.83)	<0.001	0.70
Cornell voltage, mV	24.82 (−46.47 to 96.11)	0.49	15.35 (−2.17 to 32.87)	0.09	0.66

Models were adjusted for age, sex, systolic blood pressure, body mass index, estimated glomerular filtration rate, diabetes status, and hs-Tn (except in troponin model). [a]Overall *P* values represent the difference in slopes between the TTR V142I carriers vs the noncarriers.

hs-cTnI = high-sensitivity cardiac troponin-I; mV = millivolts; TTR = transthyretin.

TABLE 4 Multivariate-Adjusted Associations Between TTR V142I Variant Carrier Status and Risk of Clinical Outcomes

	Number of Events (Rate per 1,000 Patient-Years)		Model 1		Model 2	
	V142I Variant Carriers	V142I Variant Noncarriers	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Incident HF	14 (11.2)	244 (8.3)	1.62 (0.94-2.77)	0.08	1.80 (1.07-3.05)	0.03
Overall HF hospitalization	79 (49.6)	1204 (31.8)	1.89 (1.08-3.31)	0.03	2.12 (1.23-3.63)	0.007
Recurrent HF hospitalization[a]	64 (44.1)	939 (26.1)	2.07 (1.12-3.81)	0.02	2.24 (1.22-4.12)	0.009
All-cause mortality	8 (5.2)	234 (6.4)	0.96 (0.47-1.94)	0.91	1.02 (0.52-2.00)	0.95
Incident MACE	5 (3.2)	133 (3.7)	1.01 (0.41-2.46)	0.99	0.89 (0.33-2.45)	0.83

Models were assessed by Cox proportional hazard (for incident events) or Anderson-Gill (for overall HF hospitalization and recurrent HF hospitalization) models. MACE is a composite of stroke and nonfatal myocardial infarction. Model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, systolic blood pressure, body mass index, estimated glomerular filtration rate, diabetes status, and high-sensitivity cardiac troponin. MACE is a composite of stroke and non-fatal myocardial infarction. [a]Among individuals with an incident HF event.

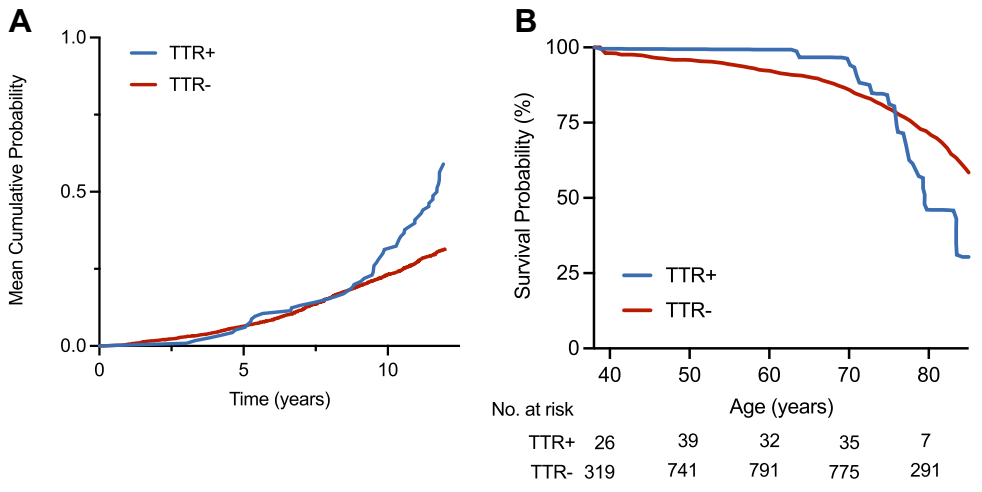
BNP = brain natriuretic peptide; HF = heart failure; MACE = major adverse cardiovascular event(s); TTR = transthyretin.

been previously reported in older cohorts (2). Future studies with longer-term follow-up of the JHS are needed to determine if the differences in HF hospitalization risk translate into differences in long-term mortality risk.

The mechanism through which TTR V142I variant carriers may have an increased risk for HF is not well understood. We observed increased levels of hs-TnI on follow-up among V142I carriers vs noncarriers. These findings suggest that V142I pathogenic variant-associated risk of HF may be driven by microvascular damage and chronic myocardial injury, which may precede LV remodeling as shown by comparable CMR parameters on follow-up in carrier vs noncarrier groups.

Our study findings have important clinical implications. In a cohort of exclusively Black adults, we observed that the TTR V142I variant may identify middle-aged individuals at an increased risk of HF on longitudinal follow-up. We also estimated mean survival time free of HF—a more intuitive and interpretable measure of risk for clinicians and patients than the previously reported HRs—among individuals with vs without TTR V142I variant. Furthermore, we observed a higher burden of chronic myocardial injury on follow-up among participants with the TTR V142I variant. These findings highlight the importance of early screening for the TTR V142I variant as a strategy to identify individuals at risk of developing downstream chronic myocardial injury and HF. This

FIGURE 2 Heart Failure-Free Survival and Cumulative Risk of Heart Failure Hospitalization Among TTR V142I Carriers Versus Noncarriers



(A) The mean cumulative probability of HF over time stratified by those with and without a TTR gene pathogenic variant. **(B)** Projected event-free survival between individuals with and without a TTR gene pathogenic variant. Age-based Kaplan-Meier estimated curves are displayed for patients aged 40 years.

TABLE 5 Comparison of Echocardiographic Characteristics and Biomarkers Among V142I Pathogenic Variant Carriers and Noncarriers Who Did Versus Did Not Develop HF on Follow-Up

Echo/Biomarker Characteristics	Participants With TTR V142I Variant			Participants Without TTR V142I Variant			*P* Value for Comparison of Columns 3 vs 6
	No HF on Follow-Up (n = 105)	HF on Follow-Up (n = 14)	*P* Value	No HF on Follow-Up (n = 2,597)	HF on Follow-Up (n = 244)	*P* Value	
Age, y	52.1 (11.2)	67.6 (4.6)	<0.01	54.0 (12.5)	64.5 (11.4)	<0.01	0.30
Men	32 (30.5)	4 (28.6)	0.99	977 (27.6)	94 (28.5)	0.83	0.64
Ejection fraction, %	62.5 ± 7.6	65.4 ± 5.0	0.17	62.3 ± 6.7	61.3 ± 8.6	0.04	0.08
LV mass indexed to BSA, g/m^2	33.4 ± 8.1	43.9 ± 9.8	<0.01	35.4 ± 8.6	41.4 ± 10.6	<0.01	0.55
Relative wall thickness	0.3 ± 0.0	0.4 ± 0.1	0.01	0.3 ± 0.1	0.4 ± 0.1	<0.01	0.36
LA diameter index, mm	17.6 ± 2.0	19.2 ± 2.1	0.04	18.0 ± 2.2	18.4 ± 2.8	0.04	0.44
LV end-diastolic volume indexed to BSA, mL/m^2	56.3 ± 9.8	64.6 ± 17.7	0.05	58.0 ± 10.1	62.5 ± 15.2	<0.001	0.72
LVOT VTI, cm/s	22.6 ± 4.0	26.1 ± 4.4	0.02	23.3 ± 4.9	24.7 ± 9.8	<0.001	0.67
E/A ratio	1.1 ± 0.3	0.9 ± 0.2	0.02	1.1 ± 0.4	1.0 ± 0.3	<0.01	0.53
TR peak velocity, cm/s	23.0 ± 8.8	27.0 ± 6.0	0.18	22.4 ± 6.9	26.3 ± 9.7	<0.01	0.83
HS-troponin, ng/L	2.8 ± 1.9, 4.2	6.0 ± 3.8, 13.5	<0.01	3.0 ± 2.2, 4.5	5.2 ± 3.5, 9.0	<0.01	0.40
BNP, pg/mL	6.9 (2.1, 15.8)	15.6 (6.1, 47.7)	0.05	6.9 (2.3, 15.1)	16.1 (6.3, 38.7)	<0.01	0.95

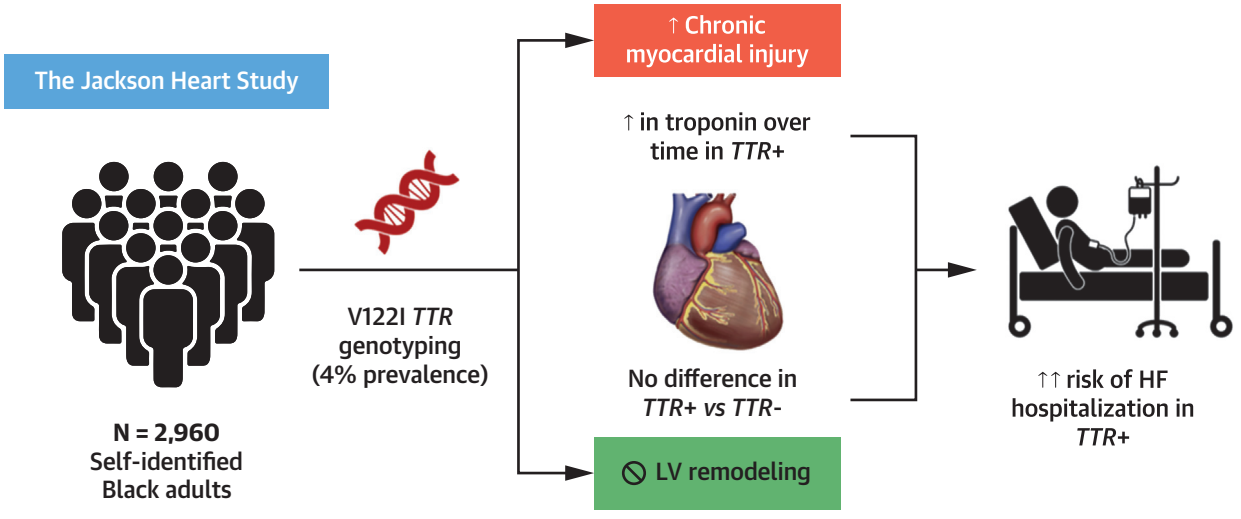
Values are n (%), mean ± SD, or median (25th percentile, 75th percentile) for hs-TnI and BNP.

BNP = B-type natriuretic peptide; E/A = ratio of peak velocity blood in early diastole (left ventricular relaxation) to peak velocity blood in late diastole (atrial contraction); LA = left atria; LV = left ventricle; LVOT = left ventricle outflow tract; TR = tricuspid regurgitation; TTR = transthyretin; VTI = velocity-time integral.

is particularly relevant considering the advancement in the therapeutic options for treating cardiac amyloidosis.

STUDY STRENGTHS AND LIMITATIONS. The strengths of our study include the relatively younger age of our study cohort, availability of cardiac biomarkers at multiple time points on follow-up, availability of echocardiographic examination at baseline, and CMR phenotyping on follow-up. Our study also has several limitations that are worth noting. Overall, the sample size of individuals with the TTR V142I variant is small, as is the number of patients undergoing CMR evaluation. In addition, data for the development of HF was obtained by

CENTRAL ILLUSTRATION Epidemiology of TTR V142I Variant in Middle Aged Self-Reported Black Adults



Coniglio, A.C. et al. J Am Coll Cardiol HF. 2022;10(2):129–138.

TTR V142I variant was prevalent in 4% of Black adults from the Jackson Heart Study. The V142I variant carrier status was associated with greater downstream burden of chronic myocardial injury, higher risk of heart failure hospitalization, and lower survival-free heart failure. There were no significant associations between V142I variant carrier status and adverse left ventricular remodeling at baseline or follow-up.

self-reporting in the first few years of follow-up, and adjudicated HF events were only available after 2005. Furthermore, the baseline echocardiographic examination did not include longitudinal strain imaging, which would be helpful in the evaluation of early signs of cardiac amyloid. However, the CMR-based examination on follow-up allowed us to compare the measures of LV strain among those with vs without the TTR V142I variant. Data for clinical manifestations of amyloid cardiomyopathy or neurologic findings of amyloidosis on follow-up were also not available. Future studies are needed to determine if early identification and treatment of TTR V142I variant carriers may modify chronic myocardial injury and HF risk trajectory.

CONCLUSIONS

Although the clinical penetrance of TTR V142I pathogenic variant among middle-aged self-reported Black individuals is low, it is associated with a lower survival free of HF and higher burden of HF hospitalization in older age. Future studies with repeated assessment of the cardiac structure, function, and longer-term follow-up on clinical events are needed to understand better the implications of the TTR V142I variant on the epidemiology of HF among Black individuals.

ACKNOWLEDGMENTS The authors thank the participants of the Jackson Heart Study for their time and participation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Jackson Heart Study was supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I), and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute and the National Institute for Minority Health and Health Disparities. Dr Hall has received support from the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant 1K08DK099415- 01A1, NIH/National Institute of General Medical Sciences grant P20GM104357, and NIH/National Institute of General Medical Sciences grant 5U54GM115428. This study was supported by research support from the Texas Health Resources Clinical Scholarship, the Gilead Sciences Research Scholar Program, National Institute of Aging GEMSSTAR grant (1R03AG067960-01), and Applied Therapeutics to Dr Pandey. Disclosures: Dr Grodin is a consultant for Pfizer, Eidos Therapeutics, and Alynlam Pharmaceuticals; and has received research funding from the Texas Health Resources Clinical Scholars fund. Dr De Lemos has received financial support from Roche Diagnostics and Abbott Diagnostics; and is a consultant for Ortho Clinical Diagnostics, Quidel, and Regeneron. Dr Berry has received financial support from Roche Diagnostics, Abbott Diagnostics, and the National Institutes of Health; is a consultant for Abbott and the Cooper Institute. Dr Butler is a consultant for Abbott, Adrenomed, Arena Pharma, Array, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cardior, CVRx, Eli Lilly, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sequana Medical, V-Wave Limited, and Vifor. Dr Mentz has received financial support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Medtronic, Merck, Novartis, Roche, Sanofi, and Vifor. Dr Sanjiv Shah has received financial support from Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and is a consultant for Abbott, Actelion, AstraZeneca, Amgen, Aria, Axon Therapeutics, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiora, CVRx, Cyclerion, Cytokinetics, Eisai, GlaxoSmithKline, Imara, Ionis, Ironwood, Keyto, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Shifamed, Tenax, and United Therapeutics. Dr Amil Shah has received financial support from Novartis through Brigham and Women's Hospital, and Philips Ultrasound through Brigham and Women's Hospital, and personal fees from Philips Ultrasound Advisory Board outside the submitted work. Dr Pandey has served on the advisory board of Roche Diagnostics; and has received nonfinancial support from Pfizer and Merck. The views expressed in this paper are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

ADDRESS FOR CORRESPONDENCE: Dr Ambarish Pandey, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390, USA. E-mail: ambarish.pandey@utsouthwestern.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among Black adults from the JHS, the *TTR* V142I variant is associated with a significantly higher burden of chronic myocardial injury and risk of HF hospitalizations.

TRANSLATIONAL OUTLOOK: Future studies are needed to evaluate whether early screening for TTR V142I variant may identify individuals who may be targeted with effective therapies to modify downstream risk of heart failure.

REFERENCES

1. Chang PP, Wruck LM, Shahar E, et al. Trends in hospitalizations and survival of acute decompensated heart failure in four U.S. communities (2005-2014): ARIC study community surveillance. *Circulation*. 2018;138:12–24.

2. Buxbaum J, Alexander A, Koziol J, et al. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies. *Am Heart J*. 2010;159:864–870.

3. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. *JAMA*. 2019;322:2191–2202.

4. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. *N Engl J Med*. 2015;372:21–29.

5. Carpenter MA, Crow R, Steffes M, et al. Laboratory, reading center, and coordinating center data management methods in the Jackson Heart Study. *Am J Med Sci*. 2004;328:131–144.

6. Taylor HA Jr, Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15:S6-4–S6-17.

7. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med*. 1999;130:461–470.

8. Fox ER, Musani SK, Samdarshi TE, et al. Clinical correlates and prognostic significance of change in standardized left ventricular mass in a community-based cohort of African Americans. *J Am Heart Assoc*. 2015;4:240–251.

9. Teichholz LE, Kreulen T, Herman MV, et al. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol*. 1976;37:7–11.

10. Fox ER, Musani SK, Bidulescu A, et al. Relation of obesity to circulating B-type natriuretic peptide concentrations in blacks: the Jackson Heart Study. *Circulation*. 2011;124:1021–1027.

11. Pandey A, Keshvani N, Ayers C, et al. Association of cardiac injury and malignant left ventricular hypertrophy with risk of heart failure in African Americans: the Jackson Heart Study. *JAMA. Cardiol*. 2019;4:51–58.

12. Patel VG, Gupta DK, Terry JG, et al. Left ventricular function across the spectrum of body mass index in African Americans: the Jackson Heart Study. *J Am Coll Cardiol HF*. 2017;5:182–190.

13. Slivnick JA, Wallner AL, Vallakati A, et al. Indexed left ventricular mass to QRS voltage ratio is associated with heart failure hospitalizations in patients with cardiac amyloidosis. *Int J Cardiovasc Imaging*. 2021;37:1043–1051.

14. Maurer MS, Koh WJ, Bartz TM, et al. Relation of the myocardial contraction fraction, as calculated from M-mode echocardiography, with incident heart failure, atherosclerotic cardiovascular disease and mortality (results from the Cardiovascular Health Study). *Am J Cardiol*. 2017;119:923–928.

15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.

16. Sigurdardottir FD, Lyngbakken MN, Holmen OL, et al. Relative prognostic value of cardiac troponin I and C-reactive protein in the general population (from the Nord-Trøndelag Health [HUNT] Study). *Am J Cardiol*. 2018;121:949–955.

17. Fox ER, Musani SK, Barbalic M, et al. Genome-wide association study of cardiac structure and systolic function in African Americans: the Candidate Gene Association Resource (CARe) study. *Circ Cardiovasc Genet*. 2013;6:37–46.

18. Jacobson DR, Alexander AA, Tagoe C, et al. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;22:171–174.

19. Keku E, Rosamond W, Taylor HA Jr, et al. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. *Ethn Dis*. 2005;15:S6-62–S6-70.

20. Zhao L, Claggett B, Tian L, et al. On the restricted mean survival time curve in survival analysis. *Biometrics*. 2016;72:215–221.

KEY WORDS amyloidosis, heart failure, survival, transthyretin V142I variant

APPENDIX For a supplemental figure and tables, please see the supplemental version of this paper.

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.