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ORIGINAL PAPER

Myocardial fibrosis by T1 mapping magnetic resonance imaging predicts incident cardiovascular events and all-cause mortality: the Multi-Ethnic Study of Atherosclerosis

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Aims To evaluate whether myocardial fibrosis predicts cardiovascular events (CVEs) and mortality in the Multi-Ethnic Study of Atherosclerosis.

Methods and results Cardiac magnetic resonance (CMR) T1 mapping with gadolinium administration for assessment of extracellular volume fraction (ECV) was performed in 1326 participants, in whom myocardial scar was assessed by late gadolinium enhancement (LGE). The clinical outcomes were defined as all-cause mortality, atherosclerotic CVEs, and incident heart failure (HF) during an average of 8 years of follow-up after the scan. Participants' mean native T1 time was 971 ms [standard deviation (SD) 45.5], ECV was 27 (SD 2.9), and 117 (8.8%) of them had LGE. At the time of the CMR exam, participant age was 68 years (SD 9) and 48% of them were women. Ideal cut-offs were identified using classification and regression trees accounting for time-to-event outcomes for ECV (30%) and native T1 time (954 ms). Over the follow-up period, 106 participants died, 78 developed CVE, and 23 developed HF. After adjustment for risk factors, ECV >30% was associated with death [hazard ratio (HR): 1.67, $P < 0.05$], incident CVE (HR: 2.02, $P < 0.05$), and incident HF (HR: 2.85, $P < 0.05$). After adjustments, native T1 >954 ms was associated with incident CVE (HR: 2.09, $P < 0.05$). Myocardial scar by LGE was not predictive of clinical outcomes after adjustments.

Conclusion ECV is an independent prognostic marker of incident HF, atherosclerotic CVEs, and all-cause mortality. ECV, with its ability to characterize both diffuse and focal fibrosis processes, better predicted incident events than regional myocardial abnormalities as visualized by LGE imaging in a large multi-ethnic population.

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Graphical Abstract

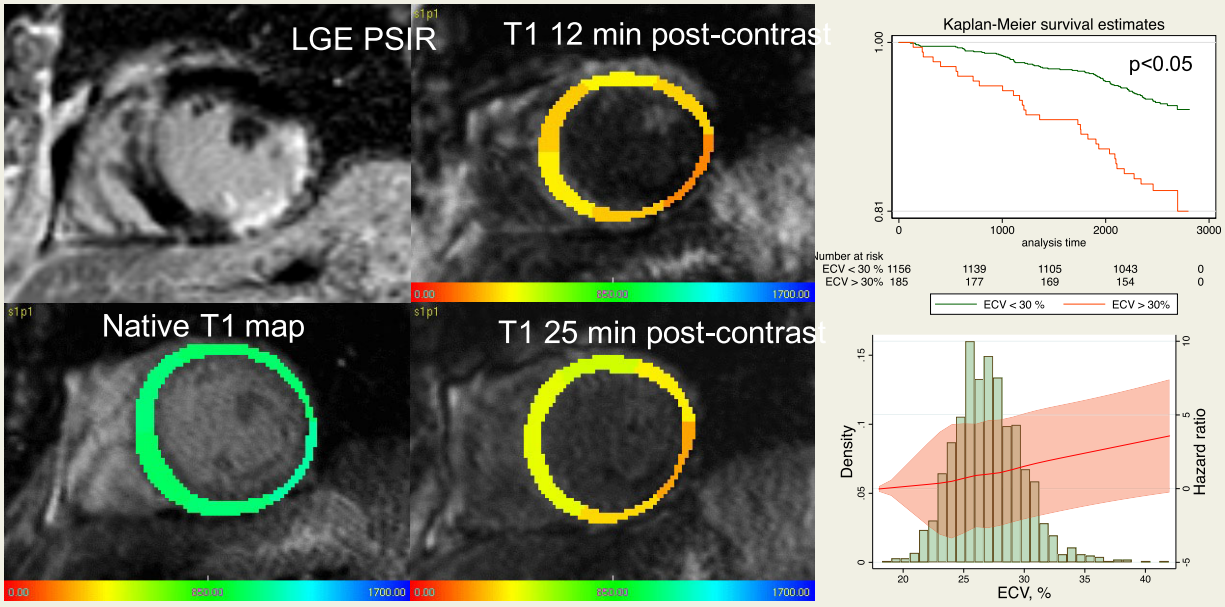

Figure showing assessment of myocardial T1 times before and after contrast administration. The corresponding short-axis late gadolinium enhancement image shows enhancement in the antero-septal and inferolateral segments. The slope between the blood R1 and the myocardial R1 over all three timepoints was used to extract the extracellular volume fraction. Plots on the right show Kaplan-Meier Survival Curves for ECV for all-cause mortality. Figure on the bottom right shows the histogram of the distribution of ECV overlaid with mortality hazard rates.

Keywords pre-contrast T1 time • extracellular volume fraction • myocardial scar • cardiovascular events • cardiac magnetic resonance

Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide, and efforts to reduce disease incidence remains a clinical challenge.[1] Cardiac magnetic resonance (CMR) imaging is a promising tool to assess myocardial functional and structural remodelling. Increased myocardial fibrosis is an important feature of myocardial remodelling, which has been shown to be associated with many CVDs, heart failure (HF), and ultimately death in different clinical settings.[2,3] In order to analyse the diverse patterns of myocardial fibrosis, novel techniques in CMR have evolved, particularly T1 mapping that allows for detailed tissue characterization.[4–6]

In this study, we used CMR to assess myocardial fibrosis in a large multi-ethnic population-based study, the Multi-Ethnic Study of Atherosclerosis (MESA), to determine whether T1 mapping-derived diffuse myocardial fibrosis assessments could be used to prognosticate incident cardiovascular events (CVEs) and mortality better than focal fibrosis assessed by late gadolinium enhancement (LGE). Previous MESA studies have found that greater diffuse interstitial myocardial fibrosis is associated with older age and remodelling.[7,8] Follow-up MESA studies have concluded that individuals with prior CVEs have a greater likelihood of diffuse myocardial fibrosis compared to their healthy counterparts, and that post-contrast T1 times show statistically significant correlations with cardiovascular risk scores.[9,10] Thus, we hypothesized that myocardial fibrosis identification and quantification by CMR through measurements of native T1 times (pre-contrast T1), extracellular volume fraction (ECV), and LGE-derived myocardial scar, will be associated with incident CVEs, HF, and all-cause death in the MESA study.

Methods

Study population

To study the pathogenesis of atherosclerosis and other CVDs, MESA enrolled 6814 individuals without baseline clinical CVD at six sites throughout the USA (Baltimore, Maryland; Minneapolis, Minnesota; Chicago, Illinois; Winston-Salem, North Carolina; New York, New York; and Los Angeles, California). Individuals from various ethnicities between the ages of 45 and 84 years old were recruited over 2 years (2000–2002).[11] In the fifth follow-up exam at Year 10 between 2010 and 2012, 3015 individuals underwent comprehensive CMR imaging, 2184 of whom completed CMR with native T1 mapping sequences. Because 41 participants had missing clinical data, the population sample for this analysis consisted of the 2143 participants who underwent CMR with T1 mapping sequences. In total, 1326 of those were also administered gadolinium for post-contrast T1 mapping and LGE assessments (*Figure 1*). Institutional

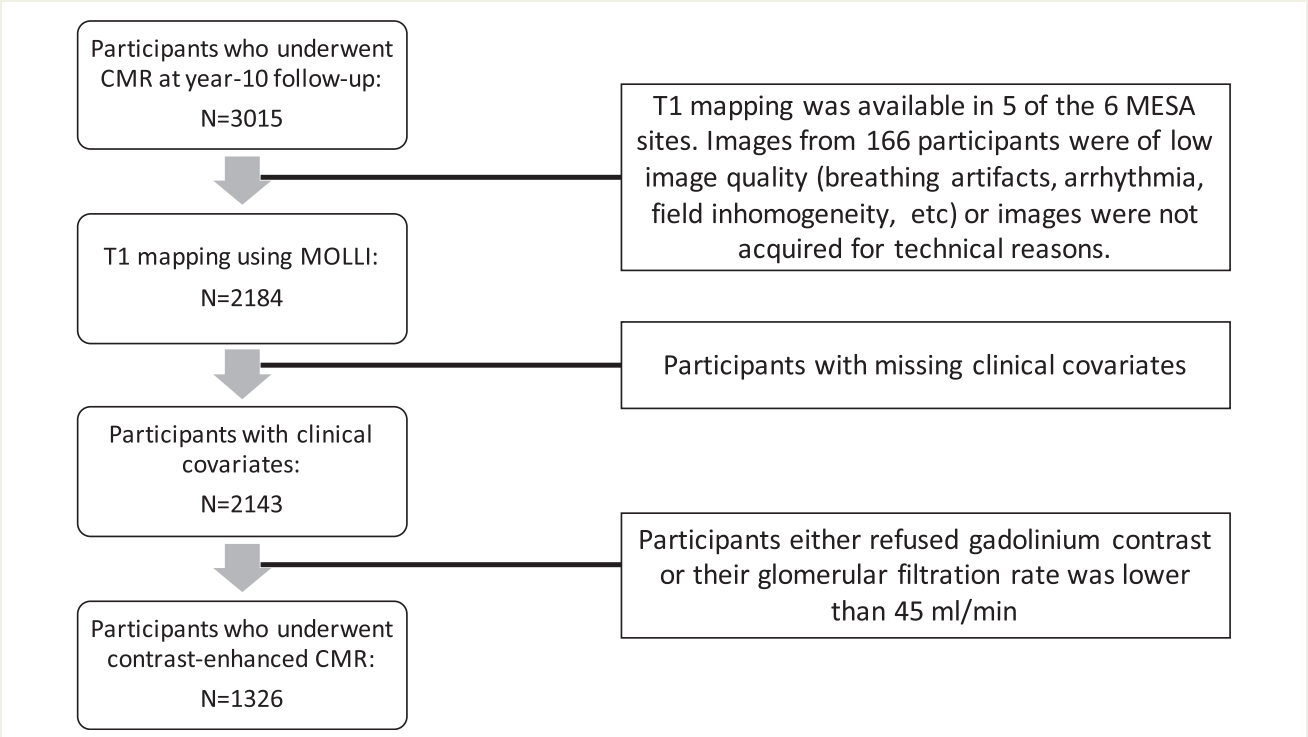

Figure 1 Flowchart delineating inclusion and exclusion criteria of the study population. CMR, cardiac magnetic resonance; MOLLI, Modified Look-Locker inversion recovery.

review boards approved the study protocol at each centre, and participants gave written informed consent.

CMR imaging

MESA participants who did not have any contraindications underwent CMR examinations with 1.5 T scanners (Avanto: Siemens Medical Systems, Erlangen, Germany) and a six-channel anterior phased array torso coil and corresponding posterior coil elements. Cine images of short-axis from above the mitral valve plane to the left ventricular (LV) apex were obtained using steady-state free precession sequences, in addition to standard four-chamber and two-chamber views. The positioning of the short-axis stack and the long-axis views were based on short-axis and long-axis scout images. CMR analysis for LV function has been previously reported.[12] The standardization of processes in CMR scanning and reading protocols in MESA, as well as the quality control processes and reader reproducibility, have been previously reported.[13]

In addition, participants with a glomerular filtration rate ≥45 mL/min (60 mL/min for Northwestern University's site) and who did not have allergies to contrast agents qualified to receive gadolinium. To assess the amount of diffuse myocardial fibrosis, T1 mapping sequences were used as follows: one short-axis pre-contrast Modified Look Locker Image (MOLLI) image at the mid-slice position, followed by repeated MOLLI acquisitions at the same slice position at 12 and 25 min following an intravenous bolus injection of gadolinium contrast at 0.15 mmol/kg (gadopentate dimeglumine; Magnevist; Bayer Healthcare Pharmaceuticals, Montville, NJ, USA).[7] Blinded researchers conducted all CMR imaging analysis. The following scanning parameters were used: flip angle = 35°; repetition time = 2.2 ms; echo time = 1.1 ms; field of view = 360 × 360 mm; matrix = 192 × 183; slice thickness = 8 mm; generalized auto-calibrating partially parallel acquisitions factor = 2.7. QMass research software (version 7.6, Medis; Leiden University Medical Center, Leiden, The Netherlands) was used to analyse T1 mapping. A three-parameter curve fit of the MOLLI source images according to the Levenberg–Marquardt algorithm were performed with automatic calculation of T1 values for the myocardium. On each T1 map (pre-contrast and post-contrast), a region of interest was manually drawn around the core myocardium to exclude the blood pool and epicardial fat to calculate the myocardial T1 time for each subject. Supplementary data online, *Figure S1* shows example region of interests (ROIs) drawn over the T1 and LGE images. The partition coefficient was determined by the slope of the linear relationship of (1/T1myo vs. 1/T1blood) at three time points—one pre-contrast and two post-contrast. ECV was then calculated by multiplying the partition coefficient by [1 - haematocrit]. However, because data on haematocrit levels at the time of CMR were not available for all participants, we also measured and validated synthetic ECV as previously described. In brief, we used a method introduced by Treibel *et al.*[14] to calculate ECV which is based on observations that haematocrit was correlated with pre-contrast T1 values of the blood pool. We performed an errors-in-variables linear regression between haematocrit as the dependent variable and pre-contrast T1 of the blood pool as the independent variable within the MESA study as detailed earlier. The resulting synthetic haematocrit values were calculated as HCTsyn = 726.19*(1/T1pre-contrast blood) - 0.07. These synthetic haematocrit values were then used for measurement of ECV. The synthetically calculated ECV and haematocrit-based ECV values were highly correlated and the difference between the two was not significant. More details on this calculation and the comparison have been previously detailed.[9] In this article, we use the synthetic-haematocrit-based ECV values for our analysis.

The presence of myocardial scar was identified as focal LGE either in two adjacent short-axis slices or in one short-axis and a long-axis

image at a corresponding location using phase-sensitive inversion recovery LGE images analysed with QMass (version 7.6, Medis) for MESA images.[15]

Clinical variables and outcomes

MESA participants underwent physical examinations and answered standardized questionnaires at all study visits to assess clinical history and cardiovascular risk factors. Traditional CVD risk factors such as hypertension, diabetes, dyslipidaemia, smoking, and age, were assessed during each visit. Every 6–9 months, participants were contacted by telephone to inquire about all interim hospitalizations, outpatient diagnosis, and deaths. Two physicians reviewed all medical records for independent endpoint classification and assignment of event dates. The outcomes included all-cause mortality, atherosclerotic CVEs (defined as MI, resuscitated cardiac arrest, angina, probable angina, stroke, stroke death, coronary heart disease death, other atherosclerotic death, and other cardiovascular death), and HF.[9] Reviewers classified HF as definite, probable, or absent. Definite or probable HF required HF symptoms, such as shortness of breath or oedema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary oedema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of LV diastolic dysfunction. We considered participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, as having no HF. In this analysis, both probable and definite HF were combined as a single endpoint.

Participants with CVD events between the cohort baseline and CMR date were included in the analysis but events prior to the CMR date were not considered outcomes. Patients with prior CVE were excluded from the analysis for CVE as the endpoint. Similarly, patients with prior HF were excluded from the analysis for HF as the endpoint. Our goal in this study was to see if ECV/native T1 were predictors of incident CVE, HF and mortality, and hence those with prior disease were excluded as appropriate for each endpoint of interest.

Statistical analysis

All categorical variables are presented as frequencies and the continuous variables are expressed as mean and standard deviation. To assess the relationship between myocardial fibrosis measures and (time to) clinical events, Cox proportional hazards models were used. Kaplan–Meier survival curves were generated to visualize how each measure of fibrosis associated with death and cardiac events over the 8-year follow-up period.

Cox regression analysis accounted for potential confounders, demographic characteristics, and traditional risk factors. Three models were generated to test the association between biomarkers of native T1, ECV, and LGE with all-cause mortality, atherosclerotic CVEs, and incident HF. Model 1 was unadjusted, Model 2 adjusted for age, gender, and race, while Model 3 adjusted for demographics as well as body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes status, smoking status, hypertension status, and lipid-lowering medication status. Classification and regression trees (CART) accounting for time-to-event outcomes were used for identifying the best cut-off for continuous predictors of outcomes—native T1 and ECV.[16]

All analyses were performed in STATA version 15.1 (Stata Corp LP, College Station, TX, USA). Two-tailed *P*-values of <0.05 were considered statistically significant.

Results

The MESA sub-population in this analysis consisted of 1326 participants with complete baseline data (CMR exam date). Participants were 48% female, 52% Caucasian, 22% African-American, 11% Chinese, and 14% Hispanic. The mean follow-up time for this study was 2394 days (standard deviation: 474 days, maximum 2803 days). The participants' mean age was 68 years at CMR date (*Table 1*). There were a total of 117 participants with LGE—of these 65 were adjudged as non-ischaemic and 52 as ischaemic by an expert radiologist.

Over the follow-up period, 106 participants died, 78 experienced CVE, and 23 experienced HF events during the follow-up period. Participants with events were on average older, were current/former smokers, diabetic, had higher systolic blood pressure, and a higher percentage were taking anti-hypertension and lipid-lowering medication. Participants with events were also less likely to be female and had a lower body mass index than the population average. Participants with events also had a higher LV mass, higher ECV and native T1 as compared to the population average. They were also more likely to have focal fibrosis as seen on LGE. In all, there were 16 prior HF events and 71 prior CVEs in the population before the CMR exam.

Association of fibrosis markers with all-cause mortality

Table 2 provides the association for each of the fibrosis markers of interest with time to all-cause mortality. Native T1 times were associated with incident mortality but this association was attenuated after adjustments for demographics. ECV was associated with time to all-cause mortality in the final multivariable model [hazard ratio (HR): 1.09 per 1%, confidence interval (CI): 1.03–1.16, $P = 0.011$]. CART analysis yielded an optimal cut-off of 30% for ECV. After adjustments for risk factors and demographics, participants who had an ECV > 30% had a higher rate of mortality as compared to those with ECV < 30% with HRs as provided (HR: 1.67, CI: 1.07–2.62, $P = 0.029$). The presence of myocardial scar as assessed visually by LGE was associated with a higher likelihood of death. However, this association was attenuated after adjustments for risk factors and demographics. *Figure 2A* shows the Kaplan–Meier curves across the high and low categories of native T1 times, indicating the higher unadjusted cumulative survival probability in participants who had a lower native T1 time as compared to those with T1 >954 ms. *Figure 3A* shows the Kaplan–Meier curves across the high and low categories of ECV, indicative of higher survival probability in participants with ECV <30% as compared to those ECV >30%. *Figure 4A* and *D* shows plots of the event HR over the range of native T1 values and ECV over the histogram of their distributions.

ECV (in %) remained significantly associated with death even after adjustment for prior CVE and HF (HR: 1.08, CI: 1.02–1.16, $P = 0.013$). However, the association of ECV >30% as a binary variable with mortality was slightly attenuated (HR: 1.56, CI: 0.99–2.47, $P = 0.054$).

Association of fibrosis markers with atherosclerotic cardiovascular events

Table 3 provides the association for each of the fibrosis markers of interest with time to incident atherosclerotic events. After adjusting

Table 1 Baseline characteristics

	Total (*N* = 1326)	Dead (*N* = 106)	Cardiovascular events (*N* = 78)	Heart failure (*N* = 23)
Age (years)	68 ± 9	77 ± 9[a]	72 ± 10[a]	74 ± 8[a]
Female gender (%)	47.7	38.9	27.5	26
Race (%)				
Caucasian	52.2	60.2	51.2	73.9
Chinese American	11.1	5.6	10.0	4.3
African American	22.9	25.9	22.5	8.7
Hispanic	13.9	8.3	16.3	13.0
Cigarette smoking (%)				
Never	42.6	31.5	31.3	26.1
Former	49.3	59.3	57.5	65.2
Current	8.1	9.3	11.3	8.7
Diabetes status (%)				
Non-diabetic	63.0	54.6	50.0	30.4
Impaired fasting glucose	21.1	23.2	20.0	39.1
Untreated diabetes	1.4	1.9	1.3	
Treated diabetes	14.5	20.4	28.8	30.4
Body mass index (kg/m^2)	28.4 ± 5.2	26.8 ± 5.3[a]	27.7 ± 4.7	27.9 ± 3.9
Systolic blood pressure (mmHg)	121 ± 19	126 ± 20[a]	128 ± 18[a]	127 ± 26
Diastolic blood pressure (mmHg)	68 ± 10	66 ± 9[a]	72 ± 9	70 ± 10
Hypertension medication (%)	49.4	63.4	65.0	73.9
Total cholesterol (mg/dL)	182 ± 36	163 ± 35[a]	172 ± 35[a]	149 ± 33[a]
HDL cholesterol (mg/dL)	54 ± 16	55 ± 16	51 ± 16[a]	50 ± 13
Triglycerides (mg/dL)	112 ± 65	95 ± 51[a]	112 ± 62	107 ± 60
Lipid-lowering medication (%)	38.1	54.6	45.0	65.2
LV ejection fraction (%)	62 ± 7	59 ± 9[a]	60 ± 8[a]	58 ± 11[a]
LV end-diastolic volume index (mL/m^2)[b]	66 ± 14	68 ± 19	65 ± 16	70 ± 21
LV mass index (g/m^2)[b]	66 ± 13	69 ± 14[a]	71 ± 13[a]	73 ± 11[a]
ECV (%)[c]	27 ± 2.9	28.6 ± 3.5[a]	27.6 ± 3.0[a]	28.9 ± 4.2[a]
Native T1 (ms)	977 ± 43	989 ± 40[a]	988 ± 40	988 ± 41
LGE detected (%)[c]	8.8	18.5	12.4	26.1
Prior CVE (%)	5.4	11.3		13.0
Prior HF (%)	1.1	5.7	2.6	

Continuous variables are represented in mean ± standard deviation. Categorical variables in percentages.
CVE, cardiovascular events; ECV, extracellular volume fraction; HDL, high-density lipoprotein; HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricle.
[a]*P*-value <0.05 in comparison with group without events.
[b]LV volumes and mass are indexed to body surface area.
[c]ECV and LGE measures were available for 1326 participant.

Table 2 Multivariable association between death and myocardial fibrosis measures

	Univariate HR (CI)	*P*-value	Model 1 HR (CI)	*P*-value	Model 2 HR (CI)	*P*-value
Native T1 (per 10 ms)	1.07 (1.02–1.11)	0.003	1.05 (0.99–1.09)	0.055	1.04 (0.99–1.09)	0.085
Native T1 > 954 ms (yes/no)	1.75 (1.09–2.82)	0.021	1.41 (0.87–2.28)	0.167	1.36 (0.84–2.23)	0.243
ECV (per 1%)	1.19 (1.12–1.25)	<0.001	1.11 (1.04–1.18)	0.001	1.09 (1.03–1.16)	0.011
ECV > 30% (yes/no)	2.64 (1.74–4.00)	<0.001	1.85 (1.21–2.82)	0.004	1.67 (1.07–2.62)	0.029
LGE (yes/no)	2.57 (1.58–4.17)	<0.001	1.47 (0.89–2.44)	0.14	1.60 (0.95–2.70)	0.079

CI, confidence interval; ECV, extracellular volume fraction; HR, hazard ratio; LGE, late gadolinium enhancement.
Number of participants for analysis, *n* = 1326 and number of events (death) = 106.
Model 1: Univariate + age, gender, and race.
Model 2: Model 1 + body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes status, smoking status, hypertension status, and lipid-lowering medication.
Models for ECV and T1 additionally included the presence of LGE as a covariate.

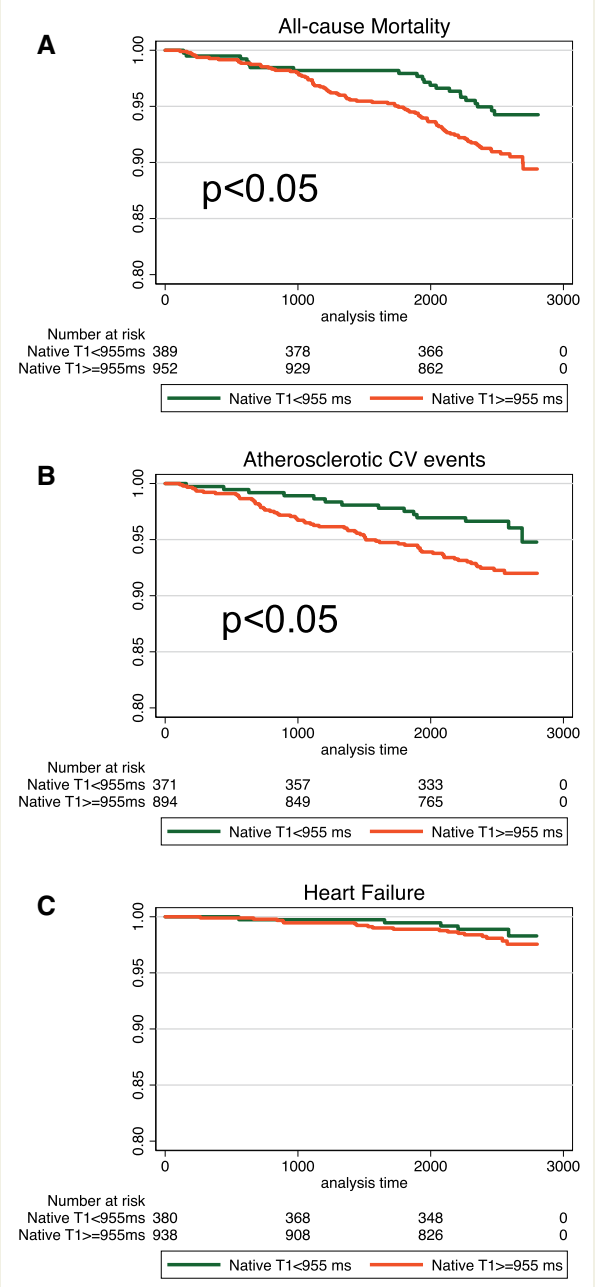

Figure 2 Kaplan–Meier survival curves for native T1 for the following grouped outcomes: (*A*) all-cause mortality, (*B*) atherosclerotic cardiovascular events, and (*C*) heart failure. Time is presented in days after the CMR scan.

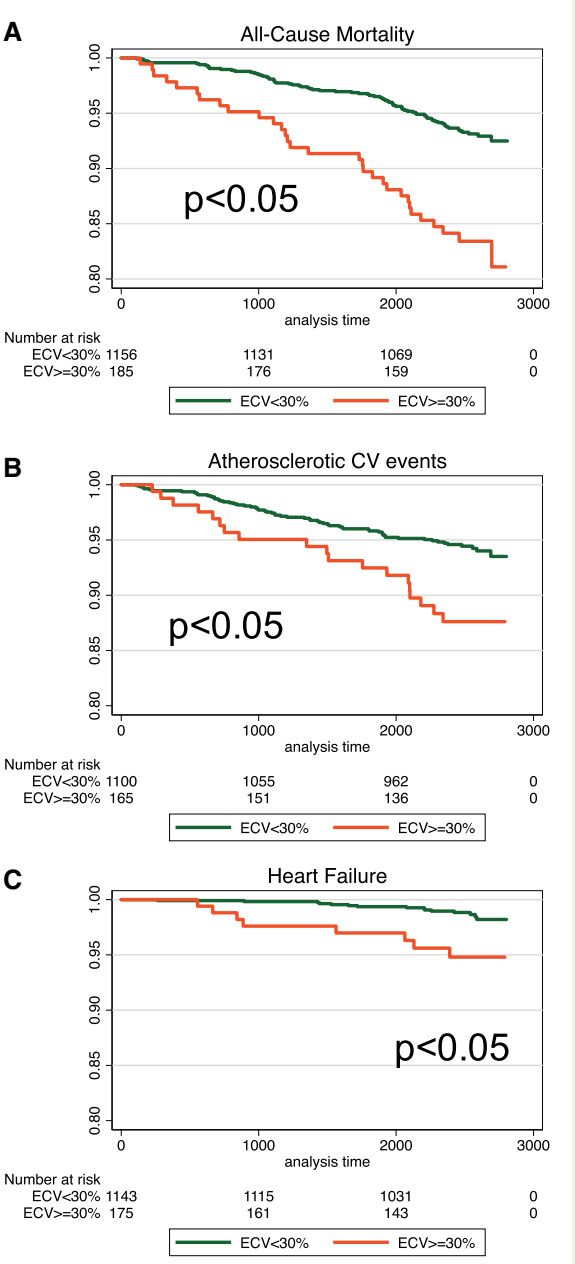

Figure 3 Kaplan–Meier survival curves for extracellular volume fraction (ECV) for the following grouped outcomes: (*A*) all-cause mortality, (*B*) atherosclerotic cardiovascular events, and (*C*) heart failure. Time is presented in days after the CMR scan.

for demographics and cardiovascular risk factors, greater native T1 was associated with higher atherosclerotic CVE rates. A 10 ms greater native T1 was associated with an 8% higher likelihood of incident CVE (HR: 1.08; CI: 1.02–1.14; $P = 0.008$). A cut-off of 954 ms was obtained by using CART analysis with CVE as the outcome and native T1 as the input. Native T1 >954 ms was also associated with a higher likelihood of incident CVE (HR: 2.09, CI: 1.15–3.81, $P = 0.016$). ECV both continuously and categorically was associated with incident CVE univariately. After adjustments, ECV >30% remained significantly associated with incident CVE (HR: 2.02, CI: 1.16–3.53, $P = 0.013$). The presence of scar by LGE was not associated with incident CVE. The Kaplan–Meier curves in *Figure 2B* shows that those with a higher value of native T1 (>954 ms) had a greater cumulative probability of having a CVE as compared to those with lower native T1 (<954 ms). *Figure 3B* similarly shows that those with ECV >30% had a higher likelihood of having a CVE during the follow-up period as compared to those with ECV <30%. *Figure 4B* and *E* shows plots of the event HR over the range of native T1 and ECV values over the histogram of their respective distributions.

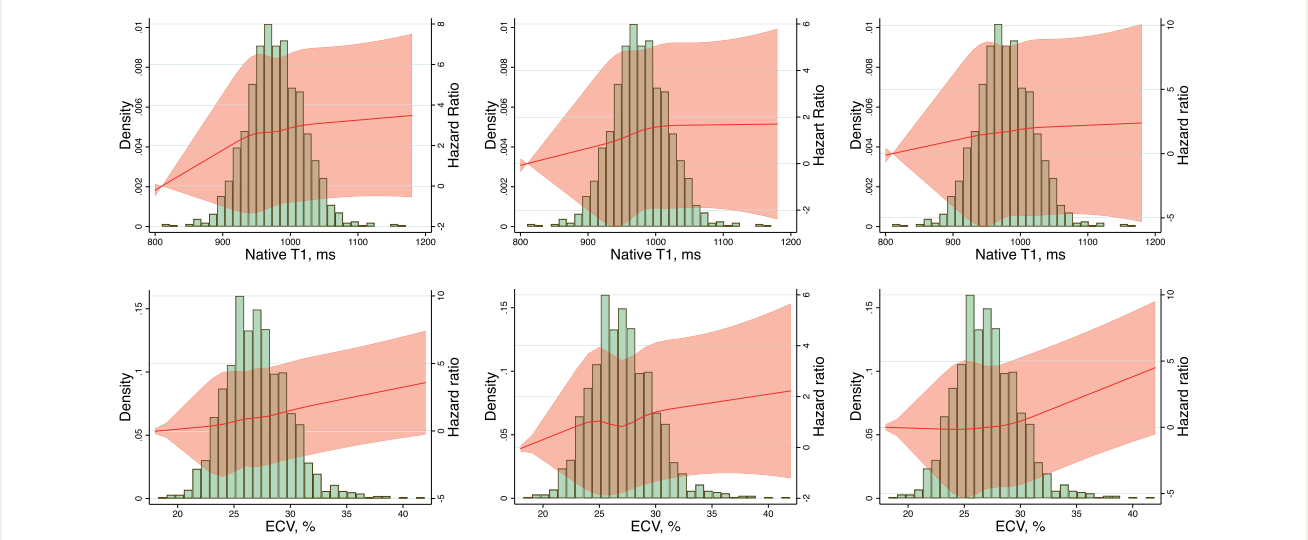

Figure 4 Histogram plots overlaid with event hazard rates illustrating both the distribution of native T1 (top row) and ECV (bottom row) and the event-specific hazard ratio over the range of values for all-cause mortality (left column), atherosclerotic cardiovascular events (middle column), and heart failure (right column).

Native T1 both as a continuous (ms, HR: 1.08, CI: 1.02–1.01, $P = 0.005$) and a categorical variable (native T1 > 954 ms, HR: 2.26, CI: 1.22–4.18, $P = 0.009$) remained significant for the prediction of CVE as the outcome even after adjustment for prior HF. ECV >30% remained independently predictive of incident CVE after further adjustment for prior HF (HR: 1.96, CI: 1.11–3.44, $P < 0.019$).

Association of fibrosis markers with incident heart failure

Table 4 provides the association for each of the fibrosis markers of interest with time to incident HF. Native T1 times were not associated with time to incident HF. ECV both as a continuous (HR: 1.20, CI: 1.05–1.37, $P = 0.011$) and categorical variable (HR: 2.85, CI: 1.19–7.29, $P = 0.033$) was associated with incident HF, even after adjustments for demographics and risk factors. The presence of myocardial scar as assessed visually by LGE was associated with a higher likelihood of incident HF. However, this association was attenuated after adjustments for risk factors and demographics. The Kaplan–Meier curves in *Figure 3B* show the clear demarcation in survival between the high and low ECV groups for HF as the outcome, with higher ECV (>30%) having a greater chance of having an HF over the follow-up period. *Figure 4F* shows plots of the event HR over the range of ECV values over the histogram of ECV distribution.

ECV remained significantly associated with incident HF even after adjusting for prior CVEs in the population both as a continuous (in %) variable (HR: 1.19, CI: 1.04–1.36, $P = 0.011$) and as a binary (ECV > 30%) variable (HR: 2.74, CI: 1.08–6.92, $P = 0.033$).

Discussion

CVD pathology often involves an increase in myocardial fibrosis, which can be either focal or diffuse in nature.[2] We studied the association of native T1 mapping, ECV and myocardial scar by LGE with incident death, atherosclerotic CVEs, and HF in a large population-based cohort. Our findings showed that greater diffuse interstitial fibrosis as assessed by ECV (optimal cut-off >30%) was independently associated with death, CVEs, and HF in MESA. In addition, native T1 was independently associated with atherosclerotic events but not with the other outcomes tested. Focal myocardial fibrosis measured using LGE-detected scar was not independently associated with outcomes in this study.

Myocardial remodelling is a consequence of several injuries from benign causes such as age to multiple-intensity myocardial injuries such as volume or pressure overload, cardiomyopathies, and ischaemic damage. Myocardial fibrosis is considered a major consequence of myocardial remodelling, and there are different fibrosis patterns observed depending on the predominant cause of myocardial injury. LGE can detect focal fibrosis caused by MI and other causes but not diffuse interstitial fibrosis. However, T1 mapping has shown to be able to accurately determine the degree of diffuse myocardial fibrosis.[17–19]

Native T1 values of the myocardium increase with higher levels of oedema, fibrosis, and inflammation (such as recent infarction), and decrease with lipid accumulation, bleeding, and iron overloading. Furthermore, recent studies have also shown that in participants suspected of having myocardial fibrosis secondary to non-ischaemic cardiomyopathies, native T1 was elevated, correlated with diffuse fibrosis and was an independent predictor of all-cause mortality.[19,20] Our results corroborate these findings, as we demonstrate that higher native T1 values are associated with worse CVD prognosis and increased mortality rates. These prior studies also showed an HR of ~1.06 to 1.1 for every 10 ms increase in native T1 for prediction of mortality, major adverse CVE, and composite HF events, which was similar to what was observed in our study. However, a direct comparison of HRs cannot be easily made given the differences in the

Table 3 Multivariable association between cardiovascular events and myocardial fibrosis measures

	Univariate HR (CI)	*P*-value	Model 1 HR (CI)	*P*-value	Model 2 HR (CI)	*P*-value
Native T1 (per 10 ms)	1.06 (1.01–1.11)	0.017	1.08 (1.03–1.14)	0.004	1.08 (1.02–1.14)	0.008
Native T1 > 954 ms (yes/no)	2.03 (1.15–3.62)	0.016	2.13 (1.18–3.83)	0.012	2.09 (1.15–3.81)	0.016
ECV (per 1%)	1.08 (1.01–1.17)	0.035	1.07 (0.99–1.16)	0.094	1.07 (0.98–1.16)	0.14
ECV > 30% (yes/no)	2.18 (1.30–3.64)	0.003	2.06 (1.21–3.51)	0.008	2.02 (1.16–3.53)	0.013
LGE (yes/no)	2.08 (1.07–4.03)	0.031	1.40 (0.71–2.77)	0.33	1.30 (0.63–2.69)	0.47

CI, confidence interval; ECV, extracellular volume fraction; HR, hazard ratio; LGE, late gadolinium enhancement.
Number of participants for analysis, $n = 1251$ and number of events (CVE) = 78.
Model 1: Univariate + age, gender, and race.
Model 2: Model 1 + body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes status, smoking status, hypertension status, and lipid-lowering medication.
Models for ECV and T1 additionally included the presence of LGE as a covariate.

Table 4 Multivariable association between heart failure and myocardial fibrosis measures

	Univariate HR (CI)	*P*-value	Model 1 HR (CI)	*P*-value	Model 2 HR (CI)	*P*-value
Native T1 (per 10 ms)	1.07 (0.97–1.17)	0.18	1.05 (0.99–1.20)	0.087	1.09 (0.97–1.21)	0.14
Native T1 > 954 ms (yes/no)	1.55 (0.57–4.18)	0.39	1.56 (0.57–4.27)	0.39	1.54 (0.55–4.30)	0.44
ECV (per 1%)	1.24 (1.10–1.40)	0.001	1.23 (1.08–1.40)	0.002	1.20 (1.05–1.37)	0.011
ECV > 30% (yes/no)	3.80 (1.61–8.96)	0.002	3.59 (1.48–8.75)	0.005	2.85 (1.19–7.29)	0.033
LGE (yes/no)	4.55 (1.79–11.56)	0.001	2.72 (1.02–7.22)	0.045	2.60 (0.95–7.15)	0.064

CI, confidence interval; ECV, extracellular volume fraction; HR, hazard ratio; LGE, late gadolinium enhancement.
Number of participants for analysis, $n = 1318$ and number of events (CHF) = 23.
Model 1: Univariate + age, gender, and race.
Model 2: Model 1 + body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes status, smoking status, hypertension status, and lipid-lowering medication.
Models for ECV and T1 additionally included the presence of LGE as a covariate.

studied population. While the two studies cited above were in patients with underlying clinical cardiomyopathy, our population was mostly devoid of overt clinical disease even though subclinical myocardial disease may not be ruled out. Native T1 times are likely to be more influenced by inflammation than ECV, and this may be what is observed. Nevertheless, given that inflammation and fibrosis are both associated with adverse outcomes, native T1 times may be more useful in patients with underlying cardiomyopathies.

Previous studies have shown that higher ECV is linked to worse CVD prognosis, increased risk of HF hospitalization, and all-cause mortality.[21–23] The strength of the findings from the previous studies indicated an HR of 1.09–1.21 per unit change in ECV for outcomes of mortality and HF, which is similar to the effect seen in our population. However, a direct comparison of the HR's cannot easily be made considering the differences in the studied populations. The findings from our study corroborate and add to these prior findings by showing that ECV greater than 30% was independently associated with incident death, CVEs, and HF. Everett *et al.*[24] showed in patients with severe aortic stenosis that ECV added prognostic information beyond LGE alone. The HR obtained for prediction of mortality was similar to that in the MESA population in spite of the differences in the population characteristics. Treibel *et al.*[14] demonstrated that ECV was not only independently associated but also improved discrimination for the prediction of HF in a large population of patients referred for CMR. Yang *et al.*[25] further extended this to include scanners of both 1.5 and 3 T field strengths in a different population, highlighting the robustness of ECV. An ECV cut-off of 31% was used to identify participants at higher risk. ECV and native T1 time are correlated, yet there are reasons which could lead to the observed differences in association seen in our study.[26] Unlike native T1, which is theorized to measure both intracellular and extracellular space characteristics, ECV is more closely correlated to the underlying extracellular myocardial fibrosis. Specifically, ECV looks at increases in collagen, mucus, gaps, and necrosis. Native T1 measurements, however, can be influenced by tissue characteristics of both the intracellular and extracellular spaces.

As previously discussed, the sensitivity of LGE-CMR is limited because it relies on image contrast between normal and fibrotic myocardium, which appear similar in cases of diffuse fibrosis.[2] LGE does not accurately visualize diffuse myocardial pathology that affects the myocardium uniformly. Hence, one possible explanation for why we did not find the same results for LGE as for ECV is that focal fibrosis (which LGE measures) is secondary to a myocardial injury, while diffuse fibrosis is secondary to remodelling. Specifically, it has been documented that although structural myocardial fibrotic remodelling initially increases tensile strength, it ultimately results in pathological

hypertrophy, muscle fibre entrapment, cell loss, and other morphologically distinct patterns of collagen accumulation that can alter muscle stiffness.[27–29] The median scar percent was 3% in our population in participants with scars. The presence of scar was also significantly lower as compared to prior studies showing independent association of LGE with events.[21,30] In addition, it has to be considered that this was a healthier population who were initially asymptomatic (at study entry). These sources of differences in pathology and population may potentially be why ECV was more significantly associated with CVEs, HF, and all-cause mortality in our study.

There has been increased interest in trying to identify agents that are capable of reversing cardiac fibrosis recently.[31] Indeed, there are numerous ongoing investigations and clinical trials. In this scenario, identification of the best technique for myocardial fibrosis assessment that aids in improved risk stratification and provides a robust endpoint for therapeutic agents targeting fibrosis is important. Recently, in patients with HF with preserved ejection fraction, pirfenidone was seen to decrease ECV.[32] This trial, among others highlights the utility of ECV as a novel endpoint. This work identifies a subgroup with higher ECV that is associated with worse outcomes. We add to current literature in efforts to identify target populations that may benefit from clinical trials focused on early therapy for reversal of myocardial diffuse interstitial fibrogenesis.

Limitations

Because the MESA cohort is a healthy population, the number of CVEs is limited, so we may require longer follow-up time to accurately assess the impact of scar and myocardial remodelling on CVEs and in particular HF. Considering the small number of HF events, the reported associations with incident HF should be interpreted with an abundance of caution. While the participants in the study were followed-up by telephone on a regular basis, advanced patient surveillance including regular chest X-rays and echocardiograms were not a part of the study protocol. A rigorous screening system would be desirable in HF focused studies. Another limitation of our study is that the population in our study composed of healthy individuals with no clinical CVD at the baseline exam, therefore, the results of our study may not be generalizable.

T1 times can vary between magnets, even when the same sequences and vendors are used.[33,34] No phantom calibration was available at the time of the 10-year follow-up exam in MESA, as a result, there is likely to be variation from the true T1 values in the final values that were used in this study. T1 and ECV values are markers of extracellular space that may be affected by extracellular space expansion due to oedema and other infiltrative processes, which are also associated with outcomes. While no known identified infiltrative diseases or myocarditis were present in this population, subclinical processes that may affect the resulting T1/ECV values cannot be ruled out. In addition, technical factors such as wall thickness, arrhythmia, anaemia, and poor breathholding are associated with both outcomes as well as variability in T1/ECV assessments. While quality control processes were put in place to control for some of these factors, influence from these factors cannot be ruled out.

In conclusion, ECV demonstrated to be an effective and independent prognostic marker of incident HF, atherosclerotic CVEs, and all-cause mortality. ECV, with its ability to characterize both diffuse and focal fibrosis processes, better predicted incident events than regional myocardial abnormalities as visualized by LGE imaging in a large multi-ethnic population.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: none declared.

Data availability

The data underlying this article were obtained as part of the NIH-sponsored Multi-ethnic Study of Atherosclerosis by permission. Data will be shared on request to the corresponding author with permission of the MESA steering committee.

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