Extracellular volume associates with outcomes more strongly than native or post-contrast myocardial T1

Thomas A. Treibel, PhD[1,2]; Yaron Fridman, MD[3,4,5,6]; Patrick Bering, MD[3,4]; Aatif Sayeed[3,4]; Maren Maanja, MD[7]; Fredrika Frojdh[7]; Louise Niklasson[7]; Eric Olausson[7]; Timothy C Wong, MD, MS[3,4,5,6]; Peter Kellman, PhD[8]; Christopher A. Miller, PhD[9]; James C. Moon, MD[1,2]; Martin Ugander, MD, PhD[7]; Erik B. Schelbert, MD, MS[3,4,5,6].

[1]Barts Heart Centre, St Bartholomew's Hospital, London, UK.
[2]Institute for Cardiovascular Science, University College of London, London, UK.
[3]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.
[4]UPMC Cardiovascular Magnetic Resonance Center, Pittsburgh, PA, USA.
[5]Heart and Vascular Institute, UPMC, Pittsburgh, PA, USA.
[6]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA, USA.
[7]Department of Clinical Physiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.
[8]National Institutes of Health, Bethesda, MD, USA.
[9]Centre Division of Cardiovascular Sciences, University of Manchester and Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

Brief Title: ECV stratifies outcome better than T1

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Correspondence:
Erik B. Schelbert, MD, MS
Director, Cardiovascular Magnetic Resonance Center, Heart and Vascular Institute, UPMC
Assistant Professor of Medicine and Clinical and Translational Science,
University of Pittsburgh School of Medicine
200 Lothrop Street, PUH A349, Pittsburgh, PA 15101, 412-647-5840; 412-647-4227 (fax)
schelberteb@upmc.edu

Objectives: Since risk stratification data represents a key domain of biomarker validation, we compared associations between outcomes and various cardiovascular magnetic resonance (CMR) metrics quantifying myocardial fibrosis (MF) in noninfarcted myocardium: extracellular volume fraction (ECV), native T1, post contrast T1, and partition coefficient.
Background: MF associates with vulnerability to adverse events e.g., mortality and hospitalization for heart failure (HHF), but investigators still debate its optimal measurements; most histologic validation data show strongest ECV correlations with MF.
Methods: We enrolled 1714 consecutive patients without amyloidosis or hypertrophic cardiomyopathy from a single CMR referral center serving an integrated healthcare network. We measured T1 (MOLLI) in noninfarcted myocardium, averaged from 2 short axis slices (basal and mid) before and 15-20 minutes after a gadolinium contrast bolus. We compared chi square (χ^2) values from CMR MF measures in univariable and multivariable Cox regression models. We assessed "dose-response" relationships in Kaplan Meier curves using log-rank statistics for quartile strata. We also computed net reclassification improvement (NRI) and integrated discrimination improvement (IDI for Cox models with ECV vs. native T1.
Results: Over a median of 5.6 years, 374 events occurred after CMR (162 HHF events and 279 deaths, 67 with both). ECV yielded best separation of Kaplan-Meier curves and highest log-ranks statistics. In univariable and multivariable models, ECV associated most strongly with outcomes, demonstrating the highest χ^2 values. Native T1 or post contrast T1 did not associate with outcomes in the multivariable model. ECV provided added prognostic value to models with native T1, e.g., in multivariable models IDI=0.0037 (95%CI 0.0009-0.0071), p= 0.02; NRI= 0.151 (95%CI 0.022-0.292), p=0.04.
Conclusions: Analogous to histologic previously published validation data, ECV myocardial fibrosis measures exhibited more robust associations with outcomes than other surrogate CMR MF measures. Superior risk stratification by ECV supports claims that ECV optimally measures MF in noninfarcted myocardium.

Key Words: Myocardial fibrosis, extracellular volume fraction, T1 mapping, extracellular matrix, cardiovascular magnetic resonance.

ABBREVIATIONS
CMR = cardiovascular magnetic resonance
CVF = collagen volume fraction
ECM = extracellular matrix
ECV = extracellular volume fraction
EF = left ventricular ejection fraction
HHF = hospitalization for heart failure
IDI = integrated discrimation improvement
LGE = late gadolinium enhancement
MI = myocardial infarction
MOLLI = MOdified Look-Locker Inversion recovery
NRI = net reclassification improvement
PSIR = phase sensitive inversion recovery

BACKGROUND

Diffuse myocardial fibrosis (MF) is a key pathological process in the heart. It predicts risk, represents a potential therapeutic target, and its measurement holds promise for future precision medicine.(1-3) MF measurement offers more complete phenotyping beyond structure, function and myocardial infarction burden. Yet multiple competing measurement techniques exist.(4-7) Identifying the optimal MF measurement technique will support risk stratification for patients, optimize design of antifibrotic trials (e.g., ability to track MF and power calculations) and facilitate biological insights. Indeed, the strength of association between MF measures and outcomes often influences causal inferences about MF and its role in the complex pathophysiology of the myocardium.

Correlation between the collagen volume fraction (CVF) and MF measures represent the histologic gold standard for MF.(8) Unfortunately, MF spatial variation throughout the myocardium can be large relative to the size of *in vivo* myocardial biopsies with a coefficient of variation of 43%(9) which greatly complicates its *in vivo* measurement. Notably, *ex vivo* whole heart MF measures from explanted hearts (in transplant recipients) yield the highest correlations between CMR MF measures and the CVF published to date.(10) Since CMR MF measures *in vivo* can quantify MF in the majority of left ventricular myocardial segments, they are less prone to confounding from spatial variation. Extracellular volume (ECV) fraction exhibits the strongest association with quantitative histologic MF measures such as the collagen volume fraction (CVF), but studies are small, and methodologies vary.(4) Other measures such as native myocardial T1, (11,12) the gadolinium partition coefficient (lambda, λ),(13) and post contrast T1 (14,15) also have been proposed as robust myocardial fibrosis measures, although each has associated limitations.(1) For example, native T1 lacks specificity for the myocardium interstitium where fibrillar collagen accumulates, lambda remains prone to hematocrit variation, and post contrast T1 remains prone to variation in: weight-based contrast dosing, timing of image acquisition post contrast, renal function, and hematocrit. In contrast, ECV reflects the volume percent of the extracellular space (including microvasculature) and is resistant to these confounders.

Native T1 generates particular interest since it requires no contrast administration. ECV and native T1 represent the principal MF measures championed by various groups as robust MF measures.

To investigate the association between outcomes and CMR MF metrics (native T1, post contrast T1, λ and ECV), we enrolled a large consecutive cohort of patients referred for clinical CMR in a single center. Reflecting the aggregate histologic validation data,(4) we hypothesized that in Cox regression models ECV would associate with outcomes (hospitalization for heart failure or death) more strongly than other quantitative CMR MF measures. Given the particular interest in native T1, which does not require contrast, we also hypothesized that ECV would associate with outcomes more than native T1 in important subgroups with or without: preserved ejection fraction, coronary artery disease, or focal myocardial damage (i.e., any myocardial infarction or focal "nonischemic" scar).

METHODS

Patient Population

After institutional review board approval, we recruited 2368 consecutive adult patients at time of clinical CMR at the UPMC CMR Center from June 1, 2010 to March 31, 2016, followed until October 11, 2018. The study complied with the Declaration of Helsinki. The cohort was formed to examine *a priori* whether novel CMR measures of MF are associated with outcomes. Inclusion criteria were: written informed consent and completion of a gadolinium contrast (Gd) enhanced CMR. Exclusion criteria included: 1) any evidence at baseline CMR for co-morbidities that lower native myocardial T1, namely iron overload (n=5) and Anderson-Fabry disease (n=3) independent of interstitial collagen concentration, 2) any evidence at baseline CMR or during follow-up for marked interstitial expansion independent of collagen, namely myocardial edema due to stress-induced cardiomyopathy (n=14), or interstitial expansion due to amyloid deposition in cardiac amyloidosis (n=68), 3) hypertrophic cardiomyopathy (n=221), a unique genetic disorder, 4) adult congenital heart disease (n=339), and 5) inadequate image quality (n=4). To maximize generalizability, we included those with acute

myocardial infarction (MI) since: a) MI size can vary greatly, b) we limited T1 and ECV measurements to remote *noninfarcted* myocardium away from the vicinity of MI or the area at risk, and c) MF in remote myocardium occurs in ischemic cardiomyopathy which can contain more collagen than the infarct itself (16). The final cohort for analysis included 1714 participants.

Data Elements

Data were managed using REDCap (Research Electronic Data Capture) hosted at the University of Pittsburgh (17) which incorporated quality checks such as missing data alerts, branching logic, and data range constraints to minimize data entry error. Baseline comorbidity data at the time of CMR were determined from the medical record. Medical record data reflect the actual data supporting medical decisions, which is relevant for generalizability. Therefore, prior heart failure diagnosis and adjudication for first HHF after CMR required documentation during the admission from physicians responsible for the patient's care. Heart failure stage was defined by practice guidelines (e.g., stage 0, not at risk for heart failure (i.e., no diabetes, hypertension, obesity, or vascular disease); stage A: at risk without structural heart disease (normal mass and volumes); B: structural heart disease without heart failure; C: structural heart disease with heart failure signs and symptoms; and D: refractory heart failure, requiring specialized support).

First HHF after CMR(18,19) included any HHF event after CMR scanning (regardless of any prior HHF), and was identified by medical record review using a definition from prior epidemiologic studies (20). HHF required physician documentation and: 1) documented symptoms (e.g., shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (e.g., edema, pulmonary rales) consistent with heart failure; 2) supporting clinical findings (e.g., pulmonary edema on radiography); or 3) therapy for heart failure, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, or beta-blockers (20). Vital status was ascertained by Social Security Death Index queries and medical record review where every death was verified in the medical record. The entire

medical record was inspected for events after CMR. Two investigators who were board certified in cardiology confirmed HHF as true HHF events (e.g., not exacerbations of primary lung disease) after detailed medical record review blinded to ECV and CMR data; there were no disagreements.

CMR Scans

Cine CMR. Patients received clinical CMR scans from a dedicated CMR center with a 1.5 Tesla scanner (Magnetom Espree, Siemens Medical Solutions) and a 32 channel phased array cardiovascular coil. Exams included standard cine imaging in long and short axis image planes with steady state free precession as described previously (21,22). Left ventricular volumes and ejection fraction (EF) were measured without geometric assumptions from short axis stacks of cines (6 mm thick, 4 mm space) by experienced readers.

Late Gadolinium Enhancement. We performed late gadolinium enhancement (LGE) imaging 10 minutes after a 0.2 mmol/kg intravenous gadoteridol bolus (Prohance, Bracco Diagnostics, Princeton, NJ) with a phase sensitive inversion recovery (PSIR) pulse sequence. We acquired employed segmented gradient echo and free breathing motion steady state free precession corrected PSIR for LGE in the same image planes used for cines.(22)

Quantification of Myocardial Fibrosis

The principal quantitative CMR MF variables were: 1) native T1, 2) post contrast T1, 3) λ, and 4) ECV (excluding any LGE). We also examined synthetic ECV (where hematocrit is estimated from blood T1 measures(23)) and ECV *including* noninfarct LGE which has been reported in prior publications.(18,24,25) We used the simple presence of noninfarct LGE as a familiar but nonquantitative comparator (26).

We employed reproducible (27) and validated(10,28,29) MOdified Look Locker Inversion recovery (MOLLI sequences) to measure T1.(24,25) All T1 related measures excluded myocardium in

the vicinity of any MI/area at risk and traced the middle third of myocardium to avoid partial volume effects. We identified MI when LGE involved the subendocardium in a typical coronary distribution, a strategy that yields sensitivities and specificities >90% for MI detection.(30)

We quantified MF with ECV defined as: $ECV = \lambda \cdot (1\text{-hematocrit})$

where $\lambda = [\Delta R1_{myocardium}] / [\Delta R1_{bloodpool}]$ pre and post gadolinium contrast (where R1=1/T1).(1)

Each T1 and ECV measurement for a short axis slice location was derived from a single native and post contrast T1 occurring after clinical LGE images (usually 15-20 minutes after contrast bolus). Hematocrit measures were acquired on the day of scanning and measured in the clinical laboratory. We averaged T1 based measures from basal and mid ventricular short axis slices to yield final measurements. Apical slices were avoided due to concerns of error related to partial volume averaging. "Synthetic ECV" employed a "synthetic hematocrit" estimated from blood T1 without direct hematocrit measurement (23) using the equation: Synthetic Hematocrit=$831.6*(1 / T1_{blood}) - 0.151$.

Statistical Analysis

We summarized categorical variables with numbers and percentages. We summarized continuous variables with medians and interquartile ranges since some variables exhibited skewed non-normal distributions based on the Kolmogorov-Smirnov test. Survival analyses examined a combined endpoint of time to either first HHF or death (all-cause mortality) since CMR measures of MF show similar relationships when each event is modeled separately.(18) Kaplan-Meier curves employed the log-rank test to illustrate "dose-response" relationships visually where each T1 based CMR MF variable was categorized into quartiles. Since T1 data exhibited skewed distributions, we also created supplemental Kaplan-Meier curves to demonstrate how risk related to the extent of deviation from normal. For each variable, strata leveraged 5 fixed equally spaced 1 standard deviation intervals of increasing fibrosis beyond the lowest quartile.

Univariable Cox regression models quantified associations between each CMR MF measure and outcomes, modeling T1 based MF measure as a continuous variable. The univariable chi square (χ^2) values tested the strength of these associations and permitted benchmark comparisons between MF measures in models where higher values equate stronger associations and lower p values. Since the units of T1 measures vary, we scaled hazard ratios to one standard deviation increments which does not affect the χ^2 values or the p values. The proportional hazards assumption for each of the CMR MF variables was confirmed by nonsignificant interactions with time. All Cox models stratified by whether CMR occurred before August 14, 2012 (epoch 1, n=945 patients) or after (epoch 2, n=483 patients). On this day, a 10 msec bias in the inversion time calculation was corrected on the scanner which could have affected T1 estimates of patients scanned thereafter. Stratification of Cox models by epoch eliminated potential confounding related to this slight change in T1 estimation. In sensitivity analyses, we repeated the Cox models limited to each epoch at a time to confirm our prior results. Multivariable Cox regression models then assessed whether univariable associations remained significant after adjustment for other confounders. We also created additional models examining the outcome of death only or HHF only (right censoring for death). Stepwise selection using a p=0.1 threshold to enter and remain in the model identified T1 MF variables associated with the composite outcome in multivariable models. Analyses were repeated for clinically important subgroups with or without: preserved ejection fraction, coronary artery disease, myocardial infarction, or any LGE.

We used integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices to evaluate the added predictive ability of Cox regression models with ECV versus Cox regression models with native T1.(31) IDI measures the new model's improvement in average sensitivity without sacrificing average specificity (analogous to the change in receiver operating characteristic curves). NRI measures the correctness of reclassification of individual subjects based on their predicted probabilities of events using the new model.(32) NRI reflects the sum of: a) the net

percentage of individuals *with events* classified at *higher risk* with the new model, and b) the net percentage of individuals *without events* classified at *lower risk* with the new model. We used the same 0.05 and 0.35 risk categories for categorical NRI published previously for ECV.(18) Statistical tests were two sided, and $p<0.05$ was considered significant. Statistical analyses were performed using SAS 9.4 (Cary, NC).

RESULTS

Patient Characteristics

Baseline characteristics of the cohort are summarized in Table 1. The median age was 57 years and 42% were women. The median ejection fraction was 57% (Q1-Q3, 45%-64%), 480 (28%) had some evidence of coronary artery disease, and 668 (39%) had focal myocardial scar evident on LGE imaging from myocardial infarction or nonischemic etiologies.

Association of Myocardial Fibrosis Metrics with Outcomes

Over a median of 5.6 years (Q1-Q3, 4.0 – 6.6 years), 374 individuals experienced events after the baseline CMR scan (162 HHF events and 279 deaths, 67 with both). Table 2 summarizes associations between MF metrics and outcome. ECV variables associated more strongly with outcomes than other variables in all univariable models as shown by χ^2 values. Post-contrast T1 was not significantly associated with outcomes, even when adjusting for variation in 1) time elapsing between contrast bolus and imaging, 2) renal function, and 3) weight. ECV also yielded the best separation of Kaplan-Meier curves in a dose dependent fashion (Figure and Supplemental Figure).

Strong associations between ECV and outcome persisted in multivariable models adjusting for several confounders as listed in Table 2. Multivariable models included only one quantitative MF metric (Table 2). Neither native T1 or post contrast T1 was significantly associated with outcomes in multivariable Cox regression models, whereas lambda associated with outcomes in both univariable

and multivariable models. The partition coefficient lambda exhibited weaker associations than ECV. The presence or absence of "nonischemic" LGE, which provided a familiar prognostic benchmark, also associated with outcomes in both models. When multivariable models included both native T1 and ECV, only ECV associated with outcomes (χ^2=35.5, HR 1.48 (95%I 1.30-1.68) per 4.0% increase (1 SD), p<0.001), whereas native T1 did not (χ^2=2.1, HR 0.90 (95%I 0.79-1.04) per 54 msec increase, 1 SD, p=0.151). Multivariable models employing stepwise selection identified ECV as the sole MF variable associated with outcomes (p<0.001) when the model included all T1 MF variables. Limiting univariable and multivariable models to epoch 1 or 2 did not change the overall results where ECV showed strongest associations with outcomes (data not shown). Similar overall trends emerged when examining the outcome of death only or HHF only, where ECV exhibited strongest associations (data not shown).

ECV provided added prognostic value compared to native T1 in Cox regression models. When compared to models with Native T1, Cox models with ECV yielded significant IDI and NRI statistics for both univariable (IDI=0.0052 (95%CI 0.0029-0.0073), p<0.001; $NRI_{continuous}$= 0.237 (95%CI 0.082-0.358), p=0.001; $NRI_{categorical}$=0.076 (95%CI 0.004-0.134), p=0.04) and multivariable models (IDI=0.0037 (95%CI 0.0009-0.0071), p= 0.02; $NRI_{continuous}$= 0.151 (95%CI 0.022-0.292), p=0.04; $NRI_{categorical}$=0.040 (95%CI 0.001-0.083), p=0.04)

Since ECV and native T1 currently represent the principal MF measures embraced by investigators, we also examined specific subgroups where we compared these measures in their associations with outcomes. Subgroups included those with or without: preserved ejection fraction, coronary artery disease, or myocardial damage (i.e., any myocardial infarction or focal "nonischemic" scar). ECV and synthetic ECV showed stronger associations with outcomes than native T1 in all univariable multivariable models.

DISCUSSION

In this cohort of consecutive patients referred for CMR, one of the largest T1 mapping cohorts reported to date, extracellular volume fraction (ECV) in noninfarcted myocardium in univariable and multivariable models exhibited the strongest associations with outcomes compared to other T1 mapping myocardial fibrosis metrics. Moreover, ECV showed a clear dose-response relationship where risk of adverse outcomes varied in proportion to extent of ECV elevation, whether ECV was "synthetic"(23) or whether or not it included noninfarct LGE(18) Since ECV with or without noninfarct LGE yielded similar hazard ratios, diffuse MF appears to associate with risk more than focal MF. In contrast to ECV, native myocardial T1, post contrast T1, the partition coefficient, and nonischemic LGE all exhibited weaker associations. ECV provided added prognostic value compared to native T1 based on IDI and NRI metrics. These robust results for ECV risk stratification mirror prior histologic validation data where ECV tends to yield highest correlations with histologic gold standards.

Association with outcomes represents an integral component of the validation for novel biomarkers that quantify biologically important disease processes. Integrating previously published data, we propose that ECV represents the most robust T1 mapping metric to quantify MF. Specifically, we note: a) the inherent specificity of ECV for the interstitial space (exploiting the extracellular nature of gadolinium contrast agents), b) the outcomes data presented herein which agrees with population studies,(33) and c) the aggregate histologic validation data reported to date suggesting ECV as the most robust MF measurement.(4) Some have articulated specific concerns about ECV measures, including the compound propagation of serial error in any one of its component measures employed in ECV computation.(6) Yet, these concerns do not diminish ECV's superior risk stratification.

Several limitations affect native T1 . Native T1 measures disease processes from whole myocardium without specificity for MF or the interstitial space. Indeed, cardiomyocytes contribute the bulk of the myocardial mass and myocardial water and therefore affect the native T1 signal. Nickander

et al. also reported that anemia and variation in the hematocrit influences myocardial native T1 measurements which include intramyocardial blood.(34) Native T1 also may be especially sensitive to off resonance due to the inability to completely shim the B0-field variation around the heart.(35) Systematic biases in T1 estimation might cancel out for ECV computations since T1 measures appear in both the numerator and the denominator.(1)

ECV also exhibits known imperfections as a MF metric. ECV may underestimate MF with high concentrations of contrast, e.g., early after a bolus. ECV, by definition, reflects the volume percent of the myocardial extracellular space and therefore lacks specificity for MF. Other conditions causing interstitial expansion, such as myocardial edema, inflammation, and amyloid fibrils, increase ECV, but ancillary clinical information often permits exclusion of these conditions. Both native T1 and ECV measures may vary across entirely different pulse sequences that have different influence from T2 or magnetization transfer. While lambda (λ) offers improved associations with outcome relative to native T1, hematocrit variation confounds lambda and diminishes risk stratification. Despite ECV's limitations, ECV may represent the most robust CMR MF metrics.

We propose that future efforts evaluating the presence and extent of MF should employ ECV if feasible. Having multiple metrics for the same biological process remains problematic since it may confuse the community and hinder translation and application. Successful translation of important biomarkers from the development community (in this case cardiovascular imagers) into the wider medical community (in this case the cardiovascular field) will enable deployment for improved diagnostics, risk stratification, and clinical trials. For serial MF measures after interventions where the cardiomyocyte and extracellular matrix compartments may each respond differently, total ECV (product of left ventricular mass and ECV) and total cardiomyocyte mass (product of left ventricular mass and (1-ECV)) measures may illuminate how each compartment responds to therapy.(3)

Limitations

Our study has limitations. First, with observational data, associations do not establish causality and may reflect unmeasured confounders. Second, although we studied a large cohort to maximize generalizability, our data reflect only single center experience. Third, we lacked histologic validation of T1 mapping parameters in our cohort, but native T1 mapping metrics of fibrosis have been validated repeatedly, and ECV consistently yields stronger associations with histological fibrosis.(4) Fourth, the T1 mapping sequences used in this cohort were upgraded during the study period, reflecting the rapid evolution in the field, but we obtained very similar significant results when examining epochs separately, and these changes would affect all T1 based measures. Fifth, the social security death index and medical record review may yield imperfect event adjudication. Still, adjudication errors would bias towards the null hypothesis and we still obtained significant results. Finally, we only used MOLLI variants at 1.5T therefore our data does not represent all currently used T1 mapping permutations.

Conclusions

The superior associations between ECV and outcomes observed in this study support prior assertions that variables beyond myocardial fibrosis may confound other T1 mapping MF measures, ultimately weakening associations with outcomes. Considering the aggregate literature, ECV might represent the superior T1 mapping metric to quantify MF based on: a) the inherent specificity of ECV for the interstitial space (exploiting the extracellular nature of gadolinium contrast agents), b) the outcomes data observed in this work and other work(33), and c) the aggregate histologic validation data reported to date. Identifying the optimal MF measurement technique will support risk stratification for patients, optimize design of antifibrotic trials (e.g., ability to track MF and power calculations) and facilitate biological insights.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

ECV as a measure of myocardial fibrosis associates most strongly with outcomes among T1 based measures. ECV might represent the superior T1 mapping metric to quantify MF based on: 1) the inherent specificity of ECV for the interstitial space, 2) robust outcomes data, and 3) prior histologic validation data.

Translational Outlook:

Identifying the optimal myocardial fibrosis measurement technique will support risk stratification, optimize design of antifibrotic trials and facilitate biological insights. The strength of outcomes associations often influences causal inferences about myocardial fibrosis and its role in the complex pathophysiology.

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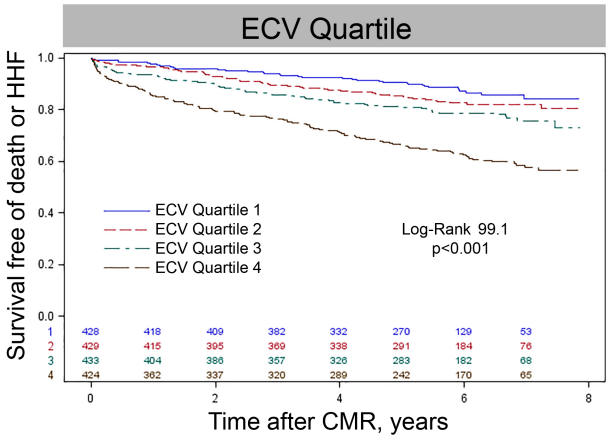
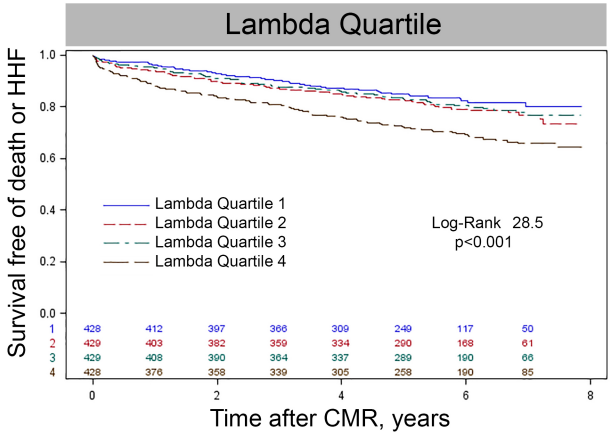
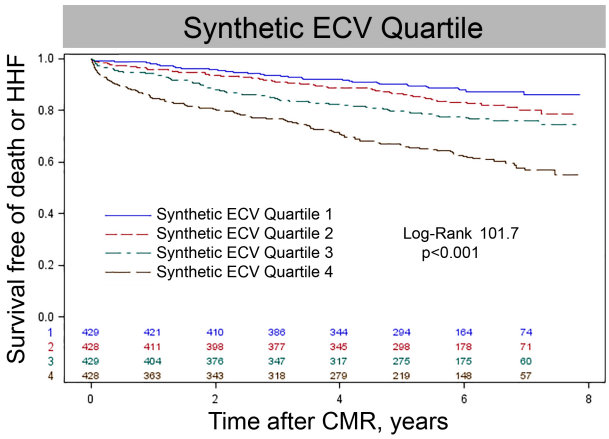
FIGURE LEGENDS

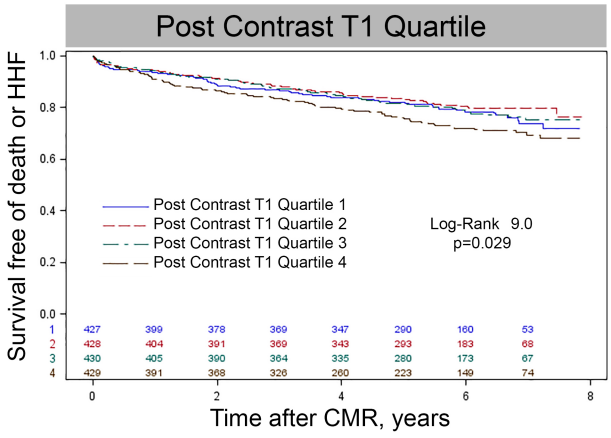
CENTRAL ILLUSTRATION: ECV exhibits more robust risk stratification than other T1-based measures of myocardial fibrosis

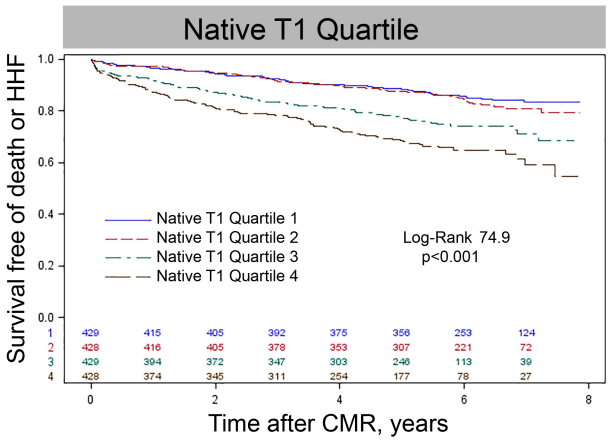
FIGURE: Kaplan-Meier plots for risk of first hospitalization for heart failure or death (n=374) in 1714 consecutive patients referred for CMR demonstrate that ECV measures MF provide the most robust risk stratification compared to native T1, partition coefficient lambda (λ), or post contrast T1 measures. In contrast to other measures, each ECV quartile yielded progressively higher event rates over time. ECV variants such as synthetic ECV (which estimates hematocrit from blood T1 measures) or ECV that included focal noninfarct scar in regions of interest yielded similar risk stratification to ECV leveraging direct hematocrit measurement that excluded foci of noninfarct scar.


ECV Quartile
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
ECV Quartile 1
ECV Quartile 2
ECV Quartile 3
ECV Quartile 4
Log-Rank 99.1
p<0.001
1 428 418 409 382 332 270 129 53
2 429 415 395 369 338 291 184 76
3 433 404 386 357 326 283 182 68
4 424 362 337 320 289 242 170 65
0 2 4 6 8
Time after CMR, years


Lambda Quartile
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
Lambda Quartile 1
Lambda Quartile 2
Lambda Quartile 3
Lambda Quartile 4
Log-Rank 28.5
p<0.001
1 428 412 397 366 309 249 117 50
2 429 403 382 359 334 290 168 61
3 429 408 390 364 337 289 190 66
4 428 376 358 339 305 258 190 85
0 2 4 6 8
Time after CMR, years


Synthetic ECV Quartile
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
Synthetic ECV Quartile 1
Synthetic ECV Quartile 2
Synthetic ECV Quartile 3
Synthetic ECV Quartile 4
Log-Rank 101.7
p<0.001
1 429 421 410 386 344 294 164 74
2 428 411 398 377 345 298 178 71
3 429 404 376 347 317 275 175 60
4 428 363 343 318 279 219 148 57
0 2 4 6 8
Time after CMR, years


Post Contrast T1 Quartile
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
Post Contrast T1 Quartile 1
Post Contrast T1 Quartile 2
Post Contrast T1 Quartile 3
Post Contrast T1 Quartile 4
Log-Rank 9.0
p=0.029
1 427 399 378 369 347 290 160 53
2 428 404 391 369 343 293 183 68
3 430 405 390 364 335 280 173 67
4 429 391 368 326 260 223 149 74
0 2 4 6 8
Time after CMR, years


Native T1 Quartile
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
Native T1 Quartile 1
Native T1 Quartile 2
Native T1 Quartile 3
Native T1 Quartile 4
Log-Rank 74.9
p<0.001
1 429 415 405 392 375 356 253 124
2 428 416 405 378 353 307 221 72
3 429 394 372 347 303 246 113 39
4 428 374 345 311 254 177 78 27
0 2 4 6 8
Time after CMR, years

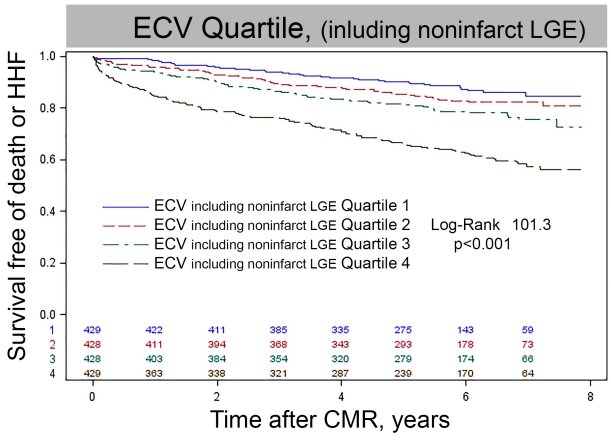

ECV Quartile, (inluding noninfarct LGE)
Survival free of death or HHF
1.0
0.8
0.6
0.4
0.2
0.0
ECV including noninfarct LGE Quartile 1
ECV including noninfarct LGE Quartile 2
ECV including noninfarct LGE Quartile 3
ECV including noninfarct LGE Quartile 4
Log-Rank 101.3
p<0.001
1 429 422 411 385 335 275 143 59
2 428 411 394 368 343 293 178 73
3 428 403 384 354 320 279 174 66
4 429 363 338 321 287 239 170 64
0 2 4 6 8
Time after CMR, years

Table 1. Baseline characteristics of 1714 consecutive patients referred for clinical cardiovascular magnetic resonance (CMR).

Variable	Summary measures
Demographics	
Age, median (Q1-Q3), y	57 (45-66)
Female, No. (%)	724 (42%)
White race, No. (%)	1506 (88%)
Black race, No. (%)	162 (9%)
*General Indication for CMR exam**	
Known or suspected cardiomyopathy, No. (%)	870 (51%)
Possible coronary disease/viability/vasodilator stress testing, No. (%)	743 (43%)
Vasodilator stress testing, No. (%)	436 (25%)
Viability assessment, No. (%)	307 (18%)
Evaluation for arrhythmia substrate*, No. (%)	579 (34%)
Post cardiac arrest evaluation	16 (1%)
Rule out ARVD evaluation	51 (3%)
Atrial fibrillation or flutter evaluation	192 (11%)
Syncope	94 (5%)
Ventricular ectopy	48 (3%)
Palpitations	196 (11%)
Sarcoidosis	75 (4%)

Valve disease assessment	129 (8%)
Pericardial disease assessment, No. (%)	66 (4%)
Possible mass or thrombus, No. (%)	87 (5%)
Thoracic aorta assessment, No. (%)	58 (3%)
Comorbidity	
Diabetes, No. (%)	342 (20%)
Hypertension, No. (%)	866 (51%)
Dyslipidemia, No. (%)	636 (37%)
Current cigarette smoking, No. (%)	244 (14%)
Prior cigarette smoking, No. (%)	510 (30%)
Atrial fibrillation or flutter, No. (%)	667 (39%)
Hospitalized/Inpatient status, No. (%)	617 (37%)
Prior percutaneous intervention, No. (%)	223 (13%)
Prior coronary artery bypass grafting, No. (%)	138 (8%)
Acute myocardial infarction, No. (%)	110 (6%)
Any evidence of coronary artery disease (ischemia, infarction, or revascularization), No. (%)	480 (28%)
Body mass index, median (Q1-Q3), kg/m^2	29 (25-34)
Weight, median (Q1-Q3), kg	86 (73-102)
Heart Failure Stage	
0	299 (17%)
A	497 (29%)
B	501 (29%)

C	417 (24%)
Medications	
ACE inhibitor, angiotensin receptor blocker, or mineralocorticoid antagonist, No. (%)	743 (43%)
Beta-blockers, No. (%)	875 (53%)
Aspirin or other antiplatelet, No. (%)	863 (51%)
Statin, No. (%)	655 (39%)
Loop diuretic, No. (%)	391 (23%)
Non-loop diuretic, No. (%)	154 (9%)
Laboratory and CMR characteristics	
Native T1 (Q1-Q3), msec	994 (963-1030)
Post Contrast T1, (Q1-Q3), msec	455 (424-486)
Time between contrast bolus and Post Contrast T1, (Q1-Q3), min	22 (20-26)
ECV (Q1-Q3), %	27.5 (25.1-30.3)
Partition coefficient lambda, λ, %	44.9 (41.9-48.5)
ECV including noninfarct LGE areas (Q1-Q3), %	27.7 (25.4-30.5)
Creatinine, median (Q1-Q3), mg/dL	1.0 (0.8-1.1)
Glomerular filtration rate, median (Q1-Q3), mL/min/1.73m^2	87 (71-98)
Hematocrit, %	39.0 (35.6-42.4)
Ejection fraction, median (Q1-Q3), %	57 (45-64)
Left ventricular mass index, median (Q1-Q3), g/m^2	56 (45-69)
End diastolic volume index, median (Q1-Q3), mL/m2	83 (67-104)

End systolic volume index, median (Q1-Q3), mL/m2	34 (25-54)
Moderate or severe mitral regurgitation by cine CMR, No. (%)	68 (4%)
Any late gadolinium enhancement, No. (%)	668 (39%)
Myocardial infarction, No. (%)	373 (22%)
Non ischemic scar evident on LGE images, No. (%)	329 (19%)

*The categories for CMR indication were not exclusive. Thus, patients could have multiple indications for CMR, and there may be overlap in the classification of indication(s).

Table 2. Among MF variables, ECV demonstrated the most robust associations with the outcome (n=374) of hospitalization for heart failure or death (all cause mortality) in univariable and multivariable Cox regression models. T1-related variables are all modeled as continuous variables, but hazard ratios are scaled to one standard deviation increments which does not affect the χ^2 values or the p values. Multivariable models adjusted for: age, gender, white race, heart failure stage, diabetes, hypertension, smoking status, prior coronary bypass surgery, prior percutaneous intervention, atrial fibrillation, moderate/severe mitral regurgitation, anemia, glomerular filtration rate, myocardial infarction, left ventricular mass/volumes indexed to body surface area, ejection fraction and stratified by epoch and hospitalization status.

Variable	Univariable model			Multivariable model		
	χ^2 value	HR (95% CI)	p value	χ^2 value	HR (95% CI)	p value
ECV, (per 4.0% increase, 1 SD)	147.9	1.74 (1.59-1.90)	<0.001	34.9	1.41 (1.26-1.59)	<0.001
Synthetic ECV, (per 4.0% increase, 1 SD)	131.9	1.70 (1.55-1.86)	<0.001	35.9	1.40 (1.25-1.56)	<0.001
Native T1, (per 54 msec increase, 1 SD)	57.7	1.45 (1.31-1.59)	<0.001	2.4	1.10 (0.97-1.25)	0.124
Post Contrast T1, (per 48 msec decrease, 1 SD)	1.5	1.07 (0.96-1.19)	0.243	1.4	0.94 (0.84-1.04)	0.237
Lambda, λ (per 5.6% increase, 1 SD)	60.7	1.45 (1.32-1.60)	<0.001	26.8	1.33 (1.19-1.48)	<0.001

Presence of noninfarct LGE	17.6	1.64 (1.30-2.07)	<0.001	4.8	1.34 (1.03-1.74)	0.029
ECV *including* noninfarct LGE areas, (per 4.1% increase, 1 SD)	149.6	1.71 (1.57-1.86)	<0.001	29.3	1.37 (1.22-1.53)	<0.001

Table 3: Compared to Native T1, ECV demonstrated more robust associations with of hospitalization for heart failure or death (all cause mortality) outcomes in univariable and multivariable Cox regression models in various important subgroups. All multivariable models adjusted for the same confounders listed in Table 2.

Subgroups	Variable	Univariable model			Multivariable model		
		χ^2 value	HR (95% CI)	p value	χ^2 value	HR (95% CI)	p value
LVEF <50% n = 547	ECV, (per 4.0% increase, 1 SD)	30.0	1.44 (1.26-1.63)	<0.001	4.7	1.21 (1.02-1.44)	0.030
Events = 207	Synthetic ECV, (per 4.0% increase, 1 SD)	22.9	1.37 (1.20-1.55)	<0.001	5.2	1.20 (1.03-1.40)	0.023
	Native T1, (per 54 msec increase, 1 SD)	2.7	1.12 (0.98-1.28)	0.100	0.1	0.97 (0.82-1.15)	0.727
LVEF ≥50% n = 1167	ECV, (per 4.0% increase, 1 SD)	84.3	1.86 (1.63-2.12)	<0.001	40.5	1.68 (1.43-1.97)	<0.001
Events = 167	Synthetic ECV, (per 4.0% increase, 1 SD)	62.7	1.77 (1.54-2.04)	<0.001	37.6	1.63 (1.40-1.91)	<0.001
	Native T1, (per 54 msec increase, 1 SD)	26.5	1.53 (1.30-1.80)	<0.001	7.3	1.31 (1.08-1.60)	0.007
CAD present n = 480	ECV, (per 4.0% increase, 1 SD)	45.7	1.67 (1.44-1.94)	<0.001	11.3	1.37 (1.14-1.65)	<0.001
Events = 174	Synthetic ECV, (per 4.0% increase, 1 SD)	35.6	1.56 (1.35-1.81)	<0.001	11.1	1.34 (1.13-1.60)	<0.001
	Native T1, (per 54	5.7	1.21	0.017	0.1	0.98	0.794

	msec increase, 1 SD)		(1.03-1.40)			(0.81-1.18)	
CAD absent n = 1234	ECV, (per 4.0% increase, 1 SD)	89.4	1.76 (1.57-1.98)	<0.001	23.7	1.46 (1.25-1.70)	<0.001
Events = 200	Synthetic ECV, (per 4.0% increase, 1 SD)	80.8	1.73 (1.54-1.95)	<0.001	23.6	1.44 (1.24-1.67)	<0.001
	Native T1, (per 54 msec increase, 1 SD)	50.6	1.57 (1.39-1.77)	<0.001	5.0	1.21 (1.02-1.43)	0.026
LGE present n = 668	ECV, (per 4.0% increase, 1 SD)	60.2	1.56 (1.40-1.75)	<0.001	15.9	1.35 (1.16-1.56)	<0.001
Events = 227	Synthetic ECV, (per 4.0% increase, 1 SD)	51.7	1.53 (1.36-1.72)	<0.001	17.2	1.34 (1.17-1.54)	<0.001
	Native T1, (per 54 msec increase, 1 SD)	22.0	1.39 (1.21-1.59)	<0.001	3.4	1.17 (0.99-1.38)	0.066
LGE absent n = 1046	ECV, (per 4.0% increase, 1 SD)	69.9	1.87 (1.62-2.17)	<0.001	20.3	1.55 (1.28-1.87)	<0.001
	Synthetic ECV, (per 4.0% increase, 1 SD)	50.0	1.72 (1.48-2.00)	<0.001	19.2	1.50 (1.25-1.78)	<0.001
Events = 147	Native T1, (per 54 msec increase, 1 SD)	23.8	1.44 (1.24-1.66)	<0.001	0.6	1.08 (0.89-1.32)	0.437
Myocardial infarction present n = 373	ECV, (per 4.0% increase, 1 SD)	41.5	1.71 (1.45-2.01)	<0.001	7.5	1.34 (1.09-1.66)	0.006
Events = 142	Synthetic ECV, (per 4.0% increase, 1 SD)	31.9	1.61 (1.37-1.90)	<0.001	7.8	1.33 (1.09-1.62)	0.005
	Native T1, (per 54 msec increase, 1	8.3	1.29	0.004	0.6	1.08	0.451

	SD)		(1.09-1.54)			(0.88-1.33)	
Myocardial infarction absent n = 1341 Events = 232	ECV, (per 4.0% increase, 1 SD)	93.2	1.73 (1.55-1.94)	<0.001	25.3	1.44 (1.25-1.66)	<0.001
	Synthetic ECV, (per 4.0% increase, 1 SD)	81.3	1.68 (1.50-1.88)	<0.001	25.9	1.42 (1.24-1.63)	<0.001
	Native T1, (per 54 msec increase, 1 SD	40.4	1.47 (1.30-1.65)	<0.001	2.5	1.13 (0.97-1.32)	0.116