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CLINICAL RESEARCH
Imaging

Prevalence and prognosis of ischaemic and non-ischaemic myocardial fibrosis in older adults

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Aims Non-ischaemic cardiomyopathies (NICM) can cause heart failure and death. Cardiac magnetic resonance (CMR) detects myocardial scar/fibrosis associated with myocardial infarction (MI) and NICM with late gadolinium enhancement (LGE). The aim of this study was to determine the prevalence and prognosis of ischaemic and non-ischaemic myocardial fibrosis in a community-based sample of older adults.

Methods and results The ICELAND-MI cohort, a substudy of the Age, Gene/Environment Susceptibility Reykjavik (AGES-Reykjavik) study, provided a well-characterized population of 900 subjects after excluding subjects with pre-existing heart failure. Late gadolinium enhancement CMR divided subjects into four groups: MI ($n = 211$), major ($n = 54$) non-ischaemic fibrosis (well-established, classic patterns, associated with myocarditis, infiltrative cardiomyopathies, or pathological hypertrophy), minor ($n = 238$) non-ischaemic fibrosis (remaining localized patterns not meeting major criteria), and a no LGE ($n = 397$) reference group. The primary outcome was time to death or first heart failure hospitalization. During a median follow-up of 5.8 years, 192 composite events occurred (115 deaths and 77 hospitalizations for incident heart failure). After inverse probability weighting, major non-ischaemic fibrosis [hazard ratio (HR) 3.2, $P < 0.001$] remained independently associated with the primary endpoint, while MI (HR 1.4, $P = 0.10$) and minor non-ischaemic LGE (HR 1.2, $P = 0.39$) did not. Major non-ischaemic fibrosis was associated with a poorer outcome than MI (HR = 2.3, $P = 0.001$) in the adjusted analysis.

Conclusion Major non-ischaemic patterns of myocardial fibrosis portended worse prognosis than no fibrosis/scar in an older community-based cohort. Traditional risk factors largely accounted for the effect of MI and minor non-ischaemic LGE.

Keywords Fibrosis • Prognosis • Gadolinium • Myocardial infarction • Non-ischaemic cardiomyopathy

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Introduction

Non-ischaemic cardiomyopathies (NICM) refer to a diverse group of diseases which can cause heart failure, arrhythmias, and death.[1,2] Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is well validated for detecting scar/fibrosis within the myocardium.[3] Specific patterns of scar/fibrosis corresponding to myocardial infarction (MI) and various NICM are diagnostically useful.[3,4] Both non-ischaemic scar/fibrosis and MI as detected by CMR have prognostic value, and recent guidelines highlight the importance of imaging myocardial fibrosis by CMR[5]. However, most prior studies have focused on tertiary care referral populations or those with pre-existing heart failure.[6–9]

In the ICELAND-MI cohort,[10] we have previously shown that participants with CMR evidence of unrecognized MI had similar mortality to participants with clinically recognized MI.[11] However, the prevalence and prognosis of scar/fibrosis from non-ischaemic aetiologies was not known in this cohort or in the general population.

Thus, the primary aim of this study was to use the ICELAND-MI cohort to determine the prevalence and prognosis of myocardial scar/fibrosis consistent with NICM as detected by LGE. Specifically, we hypothesized that major patterns of scar/fibrosis associated with NICM would portend higher risk of heart failure and death when compared with other participants.

Methods

Study participants were recruited from January 2004 to January 2007 into ICELAND-MI ($n = 936$) from the AGES-Reykjavik study ($n = 5764$), a

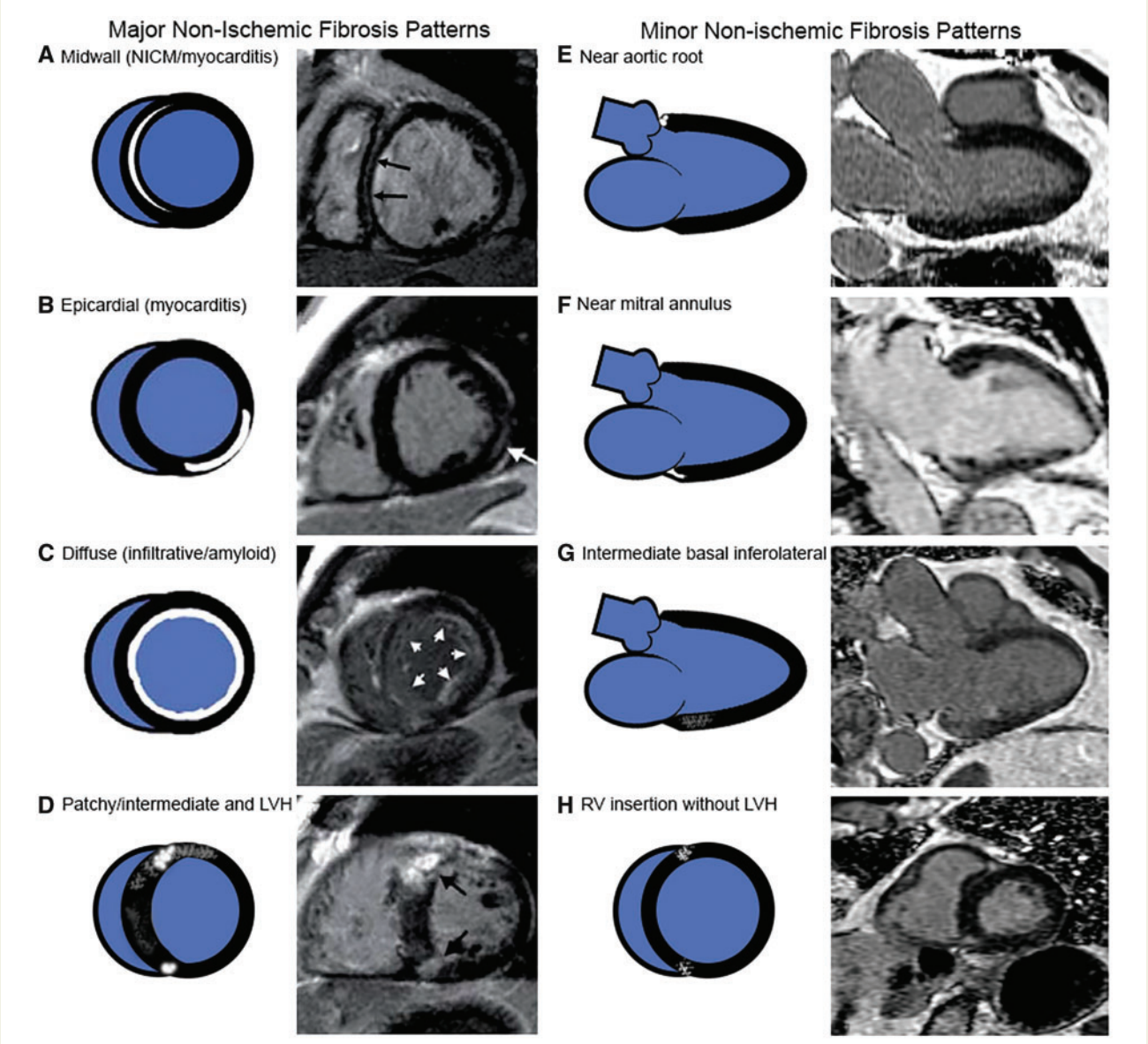


Figure 1 Categorization of non-ischaemic myocardial scar/fibrosis type.

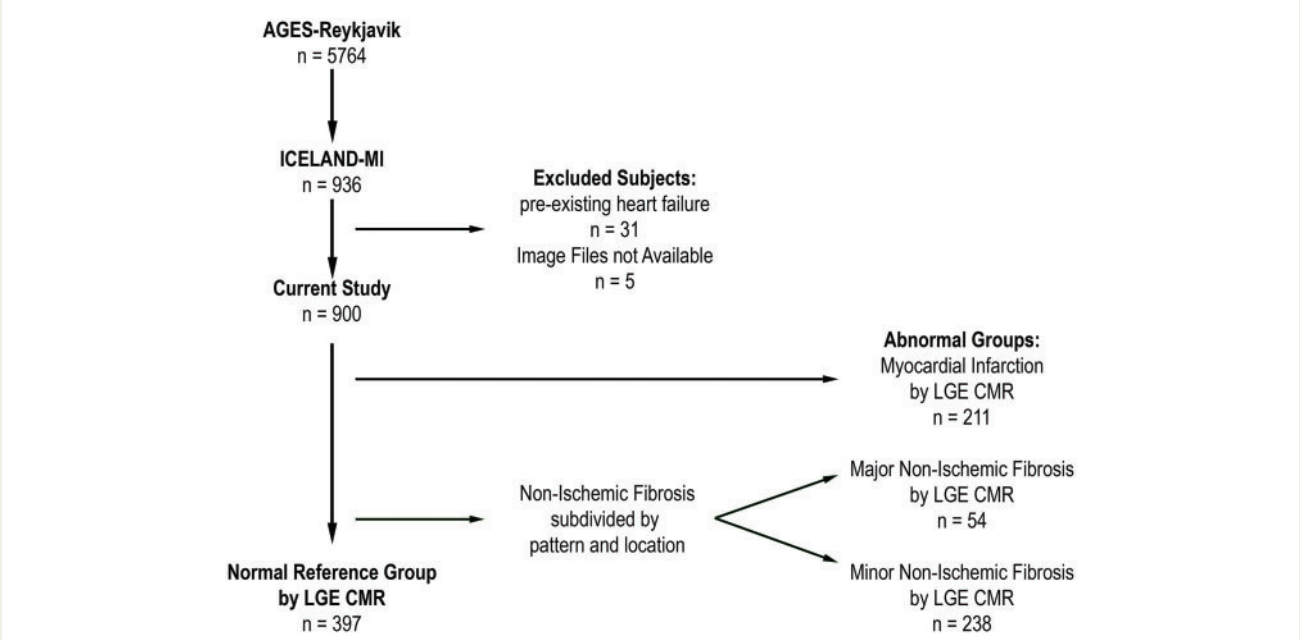


Figure 2 Study flowchart.

community-based cohort of survivors from the original Reykjavik Study born between 1907 and 1935 who were followed by the Icelandic Heart Association in Iceland since 1967.[10] Further details regarding recruitment for ICELAND-MI have been described.[11] AGES-Reykjavik and ICELAND-MI were approved by both the National Institutes on Aging intramural institutional review board and the National Bioethics Committee in Iceland which serves as the institutional review board for the Iceland Heart Association.

AGES-Reykjavik subjects who could provide written and informed consent and were deemed eligible for recruitment and were enrolled in two phases. Participants were randomly recruited for ICELAND-MI in Phase I, while Phase II preferentially recruited diabetic participants due to an under-representation in Phase I. Subjects were excluded if they could not safely undergo magnetic resonance imaging (e.g. implantable devices) or receive gadolinium contrast (e.g. severe renal disease). For this study, participants were excluded if they had missing CMR images or antecedent heart failure as incident heart failure was part of the study outcome. The AGES-Reykjavik study, which encompassed the full cohort of ICELAND-MI, recorded a large spectrum of demographics, comorbidities, clinical variables, and biochemical measurements over three clinic visits performed within a 4–6 week time window.[10,11]

Endpoint definitions

The primary study outcome was a composite of time to hospitalization for heart failure or death. All-cause mortality was determined by the national mortality index with validation performed using death certificates. Heart failure outcomes were adjudicated by a cardiologist (blinded to CMR data) using hospital discharge ICD 10 codes, which were then verified by a review of hospital records. Details of the heart failure endpoint definition have been published.[12] The analysis of the heart failure endpoint was restricted by the last available date of adjudication (31 December 2010 at time of submission). Thus, the duration of follow-up for the composite endpoint of incident heart failure hospitalization or death was limited to this date.

Cardiac magnetic resonance imaging and late gadolinium enhancement classification

Cardiac magnetic resonance exams were performed on a 1.5 T scanner (GE Healthcare) with an 8-element cardiac phased array coil. Steady-state free precession cine imaging was performed in long- and short-axis views using pixel dimensions of 1.8 × 2.1 mm, a slice thickness of 8 mm, and 30 images per cycle.

Late gadolinium enhancement images were analysed by consensus read of two cardiologists with expertise in CMR who were blinded to participant outcomes. Scar/fibrosis from MI or non-ischaemic scar was assessed using prospective, electrocardiogram-gated, segmented, phase-sensitive gradient echo inversion recovery sequence performed approximately 6–25 min after 0.1 mmol/kg intravenous administration of gadolinium (Magnevist, Berlex) contrast.

Cardiac magnetic resonance images had already been analysed for MI.[11] A new analysis assessed for non-ischaemic myocardial scar/fibrosis in all participants. No reading of MI was changed from the original analysis but presence of non-ischaemic patterns of LGE in addition to the MI was noted in the re-reading. Using standard established clinical definitions (*Figure 1*),[4] each subject was then re-categorized into one of the three following groups in a hierarchical order: (i) MI by LGE; (ii) non-ischaemic pattern of fibrosis (*Figure 1*); and no LGE as (iii) the reference group. On predefined basis of scar localization, subjects with non-ischaemic scar were further classified as having major or minor ischaemic scar (see Supplementary material online, *CMR methods material* and *Figure 2* for flowchart of CMR image scoring).

Extent of fibrosis/scar in the MI and major non-ischaemic cohort was further quantified using automated feature analysis and combined thresholding algorithm (FACT) which has been previously clinically validated.[13]

Table 1 Baseline characteristics according to ischaemic and non-ischaemic LGE pattern: the Iceland-MI study

Parameters	Unadjusted				Inverse propensity adjusted			
	No LGE ($n = 397$)	MI LGE ($n = 211$)	Non-ischaemic LGE[a] ($n = 292$)	*P*-value	No LGE ($n = 397$)	MI LGE ($n = 211$)	Non-ischaemic LGE[a] ($n = 292$)	*P*-value
Age (years)	75.0 (72.0–80.0)	77.0 (74.0–82.0)[b]	77.0 (72.0–81.0)	<0.001	76.0 (72.0–81.0)	76.0 (73.0–82.0)	77.0 (72.0–81.0)	0.60
Males (%)	35.5	63.5[b]	53.1[b]	<0.001	46.9	50.2	46.5	0.69
Weight (kg)	75.1 (66.7–84.8)	80.5 (71.4–89.3)[b]	78.2 (68.4–87.8)	0.004	75.6 (67.7–85.8)	79.3 (69.7–89.1)	76.1 (67.8–86.9)	0.10
Smoker[c] (%)	10.6	13.7	10.6	0.45	10.6	11.0	10.5	0.98
Type 2 DM (%)	25.4	46.5[b]	40.4[b]	<0.001	33.7	37.1	33.2	0.64
HTN (%)[d]	77.3	92.4[b]	83.2	<0.001	83.0	84.9	82.1	0.70
HTN med (%)	60.0	82.5[b]	63.4	<0.001	65.1	72.3	63.5	0.11
CAC[e]	5.2 (3.6–6.3)	6.8 (6.0–7.5)[b]	5.9 (4.5–6.7)[b]	<0.001	5.6 (4.2–6.7)	6.1 (4.8–7.2)	5.7 (4.2–6.7)	0.05
MI before (%)[f]	8.8	51.7[b]	10.6	<0.001	14.0	19.3	14.0	0.21
Stroke/TIA (%)	5.5	5.2	5.1	0.97	6.4	7.5	5.4	0.64
Aspirin (%)	28.2	61.6[b]	35.3	<0.001	36.2	43.7	34.6	0.11
BetaB (%)	34.5	56.4[b]	35.6	<0.001	40.1	43.0	38.3	0.58
Statins (%)	20.0	49.3[b]	25.0	<0.001	25.3	28.9	24.3	0.50
LDL (mg/dL)	134.7 (112.4–162.2)	109 (86.1–146.7)[b]	132.0 (103.7–161.4)	<0.001	130.5 (105.8–159.8)	136.3 (95.4–165.3)	133.6 (103.9–162.2)	0.91
Creatinine	0.94 (0.79–1.09)	1.02 (0.88–1.20)[b]	0.96 (0.82–1.11)	<0.001	0.97 (0.83–1.14)	0.96 (0.83–1.19)	0.94 (0.78–1.10)	0.71
LVEF (%)	63.7 (59.0–67.5)	56.7 (48.1–63.4)[b]	62.6 (58.3–66.9)	<0.001	62.7 (57.2–70.0)	62.4 (57.0–67.2)	62.8 (58.2–70.0)	0.95
LVSV (mL)	83.1 (72.1–95.8)	81.5 (72.5–99.8)	83.1 (73.6–97.6)	0.62	83.1 (71.2–97.4)	83.7 (74–104.6)	82.9 (73.4–96.1)	0.29
LV mass (g)	90.1 (76–107.5)	111.7 (92.4–138.2)[b]	111.7 (92.4–138.2)[b]	<0.001	97.6 (82.2–116.9)	101.6 (85.3–120)	94.2 (78.1–119.5)	0.05

BetaB, beta blocker; CAC, coronary calcium; DM, diabetes mellitus; HTN, hypertension; LDL, low density lipoprotein; LGE, late gadolinium enhancement; LV mass, left ventricular mass; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; TIA, transient ischaemic attack.

[a]Non-ischaemic LGE patterns consist of major non-ischaemic LGE ($n = 54$) and minor non-ischaemic LGE ($n = 238$) (see Supplementary material online, *Table S2* for pairwise comparisons).

[b]$P < 0.05$ in pairwise comparison with the reference group after Dunnett's adjustment.

[c]Smoker, active smoker.

[d]HTN, treated HTN or SBP ≥140 mmHg untreated.

[e]Natural logarithm of coronary calcium, Agatston score.

[f]MI before, past history of heart attack or myocardial infarction.

Table 2 Breakdown of death and hospitalization for incident heart failure by study group[a]

Outcome types		Non-ischaemic LGE		Ischaemic LGE	Total
	No LGE	Minor non-ischaemic LGE	Major non-ischaemic LGE	Myocardial infarction LGE	
Death	45/397	30/238	8/54	32/211	115/900
	11.3%	12.6%	14.8%	15.2%	12.8%
Hospitalization for incident heart failure	15/397	17/238	13/54	32/211	77/900
	3.8%	7.1%	24.1%	15.2%	8.6%
Primary study outcome	60/397	47/238	21/54	64/211	192/900
	15.1%	19.8%	38.9%	30.3%	21.3%

LGE, late gadolinium enhancement.
[a]Results are listed as number of events in study group/study group size and percentage. Note that events summarized in this table represent the first event. Of the 77 participants with heart failure as their endpoint, 32 eventually died. These 32 deaths are not in the table since the Kaplan–Meier method censors a patient from further analysis after meeting the study endpoint. However, the high mortality of the adjudicated heart failure endpoint is an indication that this was a relevant metric of adverse subject outcome.

Statistical analysis

Analysis was performed using SAS9.4 (Cary, NC, USA). Categorical data were presented as percentages and continuous data as median with interquartile ranges. After inspection for normality, between group differences according to LGE pattern were calculated by χ^2, one-way ANOVA, and Wilcoxon as appropriate. Pairwise comparisons to the reference group were evaluated by least square means corrected with Dunnett adjustment. The Kaplan–Meier was used to assess univariate differences in event free survival according to CMR classification. To account for baseline differences between LGE groups, a propensity score model was developed. Due to the multinomial structure (reference group, non-ischaemic LGE and MI LGE) a generalized logit model was used to calculate the probability of the observed LGE pattern. Specifics of the model development and fit statistics were supplied as Supplementary material online.

After checking assumptions, a Cox proportional hazard and Kaplan–Meier model were weighted with the inverse probability of observed LGE pattern to obtain independent risk ratio estimates and predicted survival curves for the primary endpoint according to LGE pattern. Sensitivity analyses were performed to evaluate model dependency by: (i) standard multivariable Cox regression adjusted by covariates with *a priori* prognostic presumed importance; (ii) by including extent of LGE as a linear predictor with and without an interaction term for MI LGE and major non-ischaemic LGE; and (iii) by performing a test of interaction between LGE pattern and left ventricular ejection fraction (LVEF) to evaluate if the prognostic value of LGE varied as a function of LVEF. The incremental predictive information contained in LGE category was evaluated by likelihood ratio statistics and changes in time dependent *C*-index when adding CMR findings to the other predictors in the multivariable Cox model. A two-tailed *P*-value <0.05 was required for statistical significance.

Results

Baseline characteristics and prevalence of myocardial scar/fibrosis

A total of 900 individuals were included in this study after excluding individuals with pre-existing heart failure ($n = 31$) or missing CMR images ($n = 5$). Using the defined LGE categories, the prevalence of MI was 23.4% ($n = 211$), 6.0% ($n = 54$) had a major non-ischaemic pattern of fibrosis, 26.4% ($n = 238$) had only a minor non-ischaemic pattern of fibrosis, leaving 44.1% ($n = 397$) with no LGE, constituting the normal reference group.

Most subjects in the major non-ischaemic group (88.7%) had a normal LVEF, compared with 54.5% of the participants with MI ($P < 0.001$). Severely reduced LVEF (LVEF < 35%) was found in 9% of the subjects with MI, whereas all subjects with major non-ischaemic fibrosis had LVEF >35% ($P = 0.02$).

Compared with the reference group, the non-ischaemic fibrosis group had more men, Type 2 diabetes mellitus and had higher left ventricular mass and coronary calcium scores (*Table 1*). As expected, the MI group had a risk profile consistent with ischaemic heart disease. After inverse propensity adjustment, all baseline variables were balanced across LGE categories (*Table 1*).

The most important predictors for non-ischaemic fibrosis pattern derived from the propensity model in order from strongest to weakest were left ventricular mass, diabetes mellitus Type 2, left ventricular stroke volume, coronary calcium score, and left ventricular end-systolic volume (Supplementary material online, *Table S1*). Pairwise comparisons of baseline characteristics in individuals with minor- vs. major non-ischaemic LGE are given in Supplementary material online, *Table S2*.

Prognosis of types of myocardial fibrosis as characterized by cardiac magnetic resonance

There were a total of 192 (21.3%) primary events which included 115 deaths and 77 hospitalizations for incident heart failure (details in *Table 2*). Of the subjects with heart failure, 32 (41.6%) ultimately died.

Unadjusted and inverse-propensity adjusted Kaplan–Meier curves for each of the groups were plotted with a median follow-up of 5.8 years in *Figure 3*. On univariate Cox analysis (*Table 3*), the major non-ischaemic scar/fibrosis group was at the highest risk of the primary endpoint [hazard ratio (HR) 3.5, $P < 0.001$] when compared with no LGE. The adverse event rate in subjects with MI was also significantly higher than the reference group (HR 2.5, $P < 0.001$) and minor non-ischaemic LGE (HR 1.5, $P = 0.03$). The difference between the major non-ischaemic group and subjects with MI was not

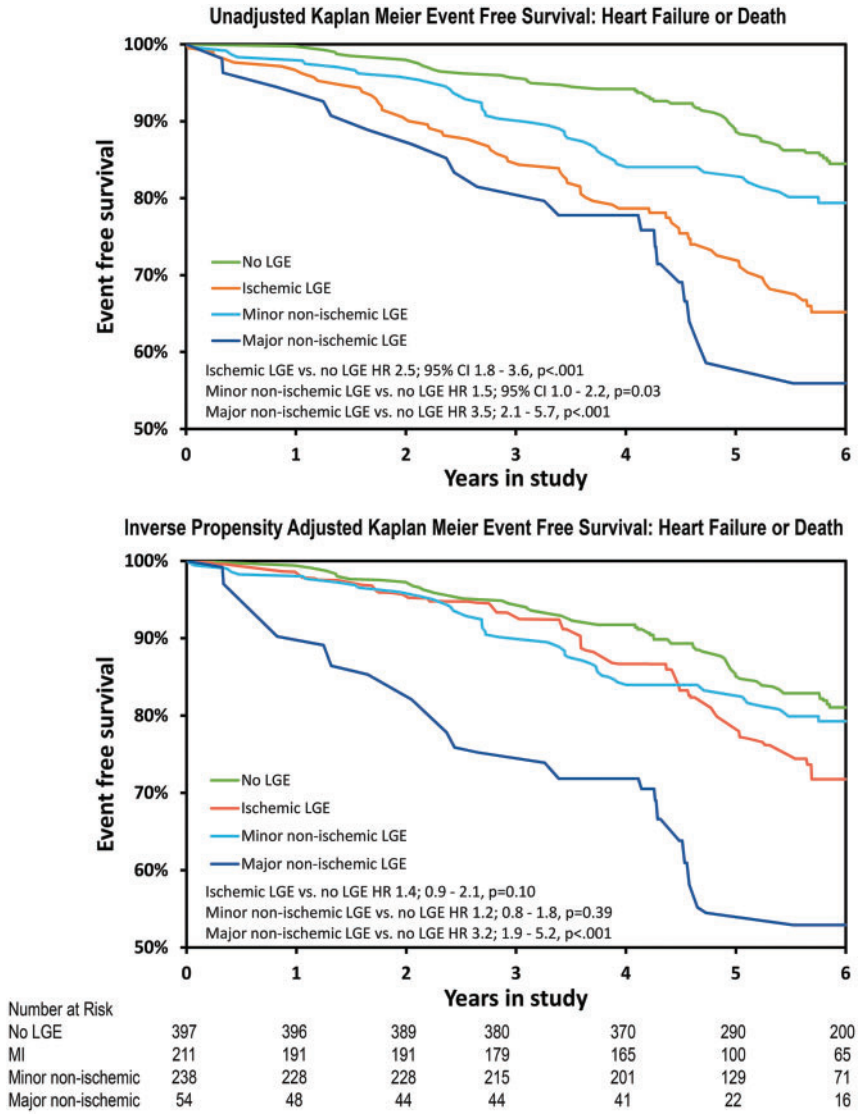


Figure 3 Unadjusted and inverse probability adjusted Kaplan–Meier estimates for the composite endpoint of heart failure or death: during a mean follow-up of 5.8 years.

statistically different ($P = 0.07$) in univariate analysis. A sensitivity analysis did not detect any significant dependency of the prognostic impact of LGE on LVEF ($P = 0.82$ for interaction).

In multivariable Cox modelling and after adjustment using inverse probability weighting (*Table 3*), major non-ischaemic fibrosis remained a strong predictor of heart failure and death (HR 3.2, $P = 0.001$) compared with no LGE. Conversely, inverse propensity adjustment accounted for the risk associated with MI (HR 1.4, $P = 0.10$) and minor non-ischaemic LGE (*Take home figure*) (HR 1.2, $P = 0.39$). Of note, major non-ischaemic fibrosis was associated with worse outcome than the MI subgroup (HR 2.3, $P = 0.001$, *Figure 3*) and minor non-ischaemic LGE (HR 2.7, $P < 0.001$) in the inverse propensity adjusted analysis.

In a separate sensitivity analysis among individuals with major non-ischaemic fibrosis or MI by LGE ($n = 253$), the amount of LGE, as a percentage of the left ventricle, was higher among patients with MI (median 10.6% of the left ventricle with interquartile range 5.6–17.6%) vs. major non-ischaemic fibrosis (median 3.0% of the left ventricle with interquartile range 3.0–5.9%, $P < 0.001$). Notwithstanding, the risk ratio for the composite outcome was comparable for individuals with non-ischaemic LGE (HR 1.13) vs. MI LGE (HR 1.01) for each 1% increase in the amount of LGE ($P = 0.14$ for interaction).

An additional sensitivity analysis was performed classifying near aortic root and mitral annular fibrosis as the midwall/epicardial pattern of fibrosis (classified under major non-ischaemic patterns of fibrosis) to address concerns that these patterns may overlap. Despite the small sample size of this group, the event-free survival of the midwall/subepicardial pattern of fibrosis differed significantly from that of the aortic and mitral annular fibrosis group and explained most of the effect on the composite group. This annular fibrosis group alone

Table 3 Univariate and adjusted hazard ratios for first of heart failure or death according to LGE pattern[a]

Variables	Univariates			Multivariates			Inverse propensity adjustment		
	HR (95% CI)	χ^2	*P*-value	HR (95% CI)	χ^2	*P*-value	HR (95% CI)	χ^2	*P*-value
Ischaemic or non-ischaemic LGE	2.1 (1.6–2.9)	23.0	<0.001	1.6 (1.1–2.2)	7.6	0.006	1.5 (1.0–2.0)	4.7	0.03
Ischaemic LGE	2.5 (1.8–3.6)	26.2	<0.001	1.4 (1.0–2.2)	3.0	0.08	1.4 (0.9–2.1)	2.7	0.10
Non-ischaemic LGE	1.8 (1.3–2.6)	11.8	<0.001	1.7 (1.2–2.4)	7.9	0.005	1.5 (1.0–2.2)	4.5	0.03
Minor non-ischaemic LGE	1.5 (1.0–2.2)	4.7	0.03	1.5 (1.0–2.2)	3.9	0.05	1.2 (0.8–1.8)	0.8	0.39
Major non-ischaemic LGE	3.5 (2.1–5.7)	23.8	<0.001	2.3 (1.4–3.9)	10.7	0.001	3.2 (1.9–5.2)	20.4	<0.001
Age (per 10-years older)	2.9 (2.2–3.7)	64.9	<0.001	2.9 (2.2–3.8)	56.2	<0.001	NA	NA	NA
Current smoker	1.8 (1.2–2.6)	9.1	0.003	2.2 (1.5–3.2)	16.7	<0.001	NA	NA	NA
Male gender	1.5 (1.1–2.0)	7.3	0.007	1.1 (0.8–1.6)	0.7	0.41	NA	NA	NA
HTN	2.3 (1.4–3.7)	11.3	<0.001	1.8 (1.1–3.0)	5.6	0.02	NA	NA	NA
LVEF (per 10% lower)	1.3 (1.2–1.5)	15.8	<0.001	1.2 (1.1–1.4)	6.9	0.009	NA	NA	NA
MI before[b]	1.7 (1.2–2.3)	9.9	0.002	1.1 (0.8–1.6)	0.2	0.62	NA	NA	NA
Log-coronary calcium	1.2 (1.1–1.3)	25.9	<0.001	1.1 (1.0–1.2)	3.2	0.07	NA	NA	NA

CI, confidence interval; HR, hazard ratio; HTN, hypertension; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NA, not applicable.
[a]Multivariable associations of non-LGE covariates reflects adjustment by LGE as ischaemic, minor- or major non-ischaemic.
[b]MI before, in the past 5 years: has a doctor or other health professional told you that you had a heart attack or myocardial infarction?

performed similarly to the other minor non-ischaemic patterns, and overall did not change the main results (see Supplementary material online, *Figures S9* and *S10*).

In subgroup analysis of all-cause mortality, both MI by LGE (HR 2.4, $P < 0.001$) and major non-ischaemic scar by LGE (HR 2.4, $P = 0.005$) were associated with higher mortality compared with the reference group on univariate analysis while minor non-ischaemic LGE was not (HR 1.4, $P = 0.13$, *Figure 4*). However, in the inverse propensity-adjusted analysis only major non-ischaemic LGE (HR 2.3, $P = 0.007$) portended an increased risk of mortality (*Figure 4*).

Ranked by χ^2, LGE pattern was the third strongest predictor of the composite endpoint after age and current smoking in a multivariate Cox model (*Table 3*). The addition of LGE pattern to standard risk factors in the multivariable Cox model resulted in a significant increase in likelihood ratio ($\Delta\chi^2$ 11.7, $P = 0.009$) and time-dependent area under curve (AUC) ($\Delta \sim 0.02$, $P < 0.001$, Supplementary material online, *Figures S6* and *S7*).

Discussion

This is the first population-based study to demonstrate that individuals with either non-ischaemic or ischaemic myocardial fibrosis/scar have worse prognosis than those without myocardial scar in older adults without pre-existing heart failure. Equally important, the risk for heart failure and death associated with non-ischaemic scar as detected by LGE CMR was worse than that of MI after propensity score adjusting for baseline characteristics including LVEF, left ventricular mass, and traditional cardiovascular risk factors. This further suggests that the pathophysiological process resulting in non-ischaemic scar is distinctly different from ischaemic scar and is associated with poor prognosis which is incompletely unaccounted for by traditional cardiac risk factors for coronary artery disease. As such, non-ischaemic scar added incremental predictive information of the primary outcome and had the highest χ^2 value in multivariable models aside from age and current smoking status. Finally, this prospective cohort also allowed determinations of the prevalence of myocardial fibrosis in the community. Thus, this work is an important and complementary step beyond prior referral centre studies of non-ischaemic myocardial scar.

It is important to note that increased left ventricular mass was the single strongest predictor of major non-ischaemic LGE. Whether preventing left ventricular hypertrophy would improve the prognosis in these patients with non-ischaemic LGE is untested since a high percentage of this population was already on treatment for hypertension. Also of note, non-ischaemic scar was a stronger predictor of death or heart failure than LVEF. This may be partially explained by the observation that LVEF tended to be low in patients with MI but most patients with non-ischaemic fibrosis had preserved systolic function.

Newer T1 mapping methods may be more sensitive in detecting diffuse interstitial fibrosis than LGE imaging.[14] Thus, LGE likely represents only a fraction of the extent and severity of the underlying fibrosis in these NICM. These techniques have the potential to offer further insight into non-ischaemic aetiologies. A few studies demonstrate prognostic significance associated with changes in native myocardial T1 or extracellular volume fraction.[15,16] These methods were not available at the time of the ICELAND-MI study. Furthermore, these T1 mapping techniques are not yet widely available. The referral centre studies quoted earlier[6–8] used simple LGE to detect myocardial fibrosis, a methodology that is widely distributed that has approximately 15 years of clinical experience.

Specific patterns of scar/fibrosis can distinguish between different aetiologies of cardiomyopathy and thus are clinically useful (*Figure 1*).[4,17] LGE closely correlates with collagen scar in chronic MI.[3,18] Fibrosis caused by MI follows a coronary artery territory and spreads from the subendocardial layer outward towards the epicardium, a pattern recognizable on LGE CMR scans.[19] In NICM, multiple mechanisms lead to LGE in patterns distinguishable from MI

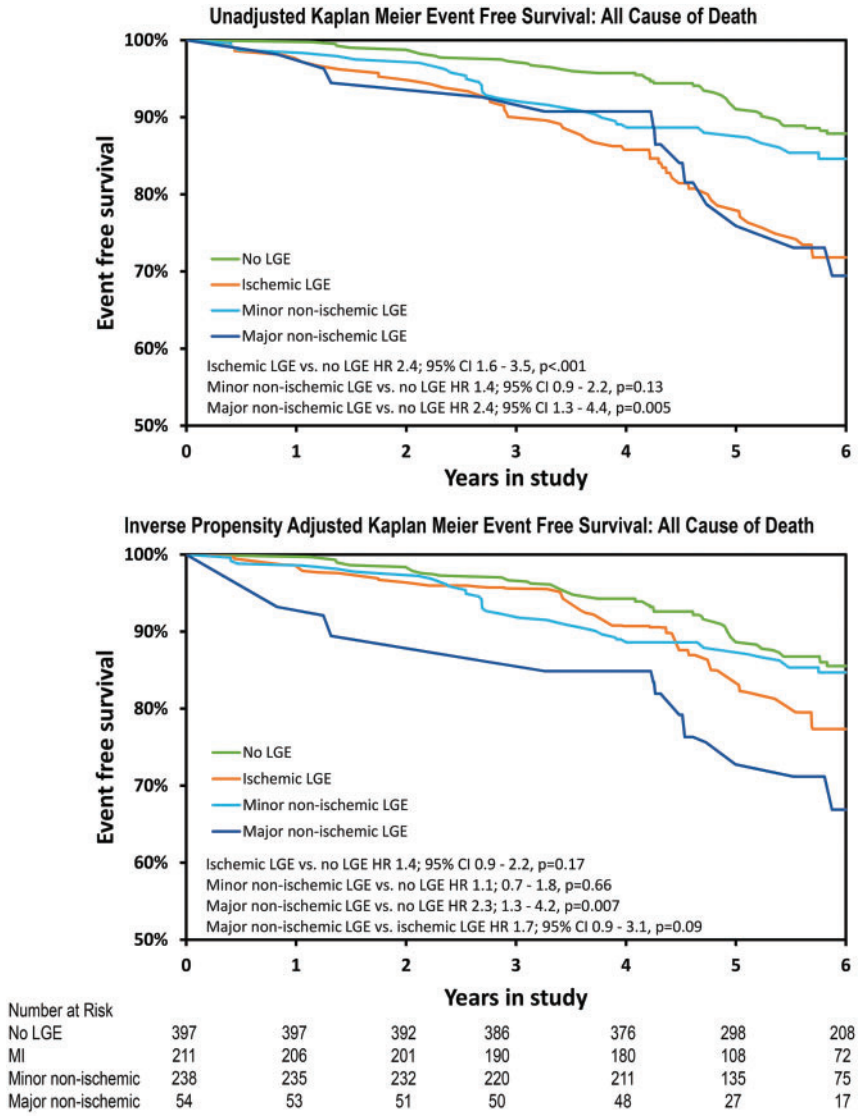
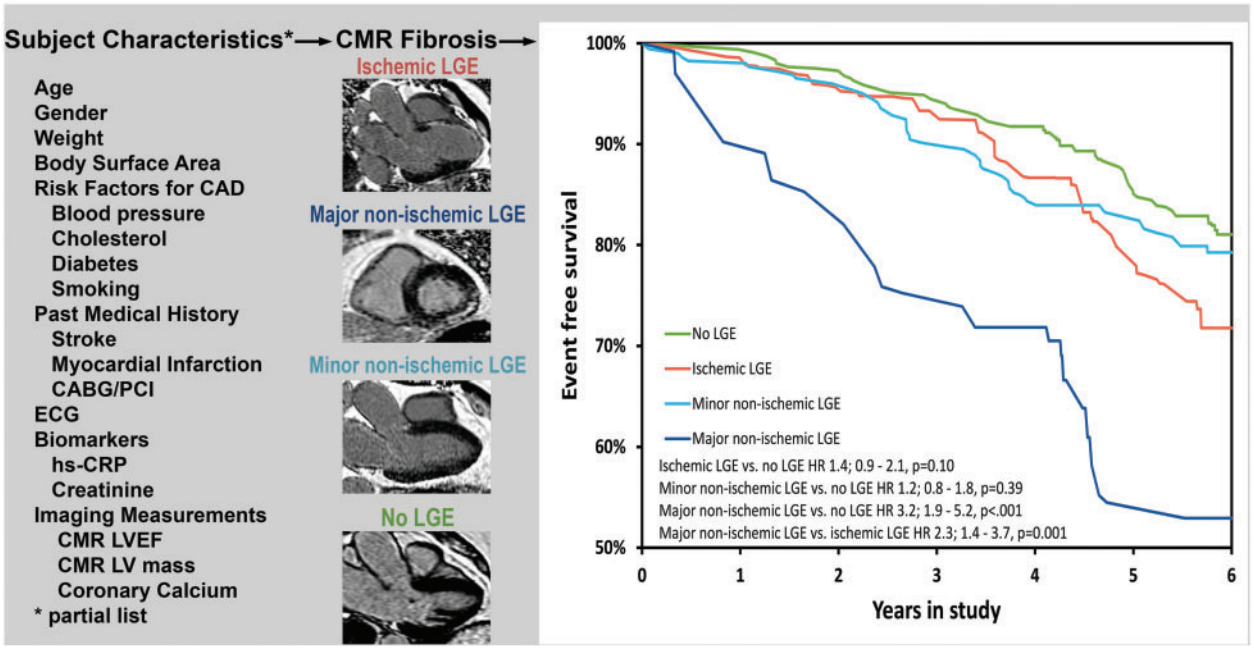


Figure 4 Unadjusted and inverse probability adjusted Kaplan–Meier estimates for all-cause mortality: during a mean follow-up of 5.8 years.

(*Figure 1*). These mechanisms include replacement fibrosis, myocardial necrosis, myocyte apoptosis, and expansion of the extracellular space as a result of infiltrative disorders. Strictly speaking, LGE in patients with amyloidosis should not be equated with fibrosis. This distinction did not affect the study as no cases of amyloidosis were encountered.

Beyond the well-established major patterns of non-ischaemic fibrosis, we encountered patterns of localized scar, which were relatively prevalent in this older population. LGE findings near the mitral and aortic valve may be explained by fibrosis in myocardium adjacent to a calcified mitral annulus or calcified aortic valve.[20–26] Extension of calcification, inflammation and fibrosis from aortic and mitral annular calcification has been demonstrated on necropsy which in severe cases has resulted in heart block secondary to disruption of the bundle of His.[27,28] The prevalence of aortic sclerosis in population studies is estimated to be 25% in those >65 years and climbs to 50% after 85 years of age.[29] Mitral annular calcification has been demonstrated to be as high as 55%[30] it is not surprising that the most frequently encountered patterns of fibrosis were localized along the valve planes. We also observed fibrosis at the right ventricular (RV) insertion points which has been previously described predominantly in the setting of pulmonary hypertension, hypertrophic cardiomyopathy, and RV hypertrophy.[31,32] LGE near the RV insertion points may also be linked to other conditions associated with advanced age since most of our participants did not have signs of pulmonary hypertension or pathological hypertrophy. Focal regions of fibrosis have been described in multiple autopsy series, and the prevalence increases with age.[33] Although their aetiology is uncertain, they are unrelated



Take home figure Inverse propensity adjusted prognosis of ischaemic and non-ischaemic myocardial fibrosis.

to coronary stenosis and may be due to metabolic processes or rheumatic diseases.[34] Thus, there are many possible pathologic correlates to the minor patterns of fibrosis seen in this study.

Study limitations

The results of this study are most applicable to Caucasian subjects and may need testing in other ethnicities. The generalizability is also limited by the advanced age of this cohort which inherently introduces survivor bias. The sensitivity of detecting fibrosis may be reduced as a result of the dose of gadolinium contrast (0.1 mmol/L/kg) used. This effect was compensated by the use of phase-sensitive inversion recovery imaging which provided better signal-to-noise ratios than what was commercially available at the time of study recruitment. The study was underpowered to study differences between groups so one should not over-interpret statistically non-significant comparisons. Additionally, this study was underpowered to evaluate differences between the individual patterns of non-ischaemic scar. Adjustment for some MI-associated risk factor covariates (e.g. smoking, which is strongly associated with MI) may have led to an overfitted model, making direct comparisons of adjusted HRs for ischaemic and non-ischaemic scar groups difficult.

Conclusion

Major non-ischaemic fibrosis/scar, as detected by LGE on CMR, was associated with a significantly greater risk for death or heart failure hospitalization than no fibrosis/scar in older community-dwelling persons without pre-existing heart failure. Major non-ischaemic fibrosis/scar portended worse prognosis than ischaemic scar in adjusted analyses.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Assurances

(1) The study was approved by the IRB for the NIA/NIH and for the National Bioethics Committee in Iceland, which serves as the IRB for the Iceland Heart Association (Methods, Paragraph 1).
(2) Data analysis was performed by the following authors: Shanbhag, Greve, Aspelund, Schelbert, Cao, Danielsen, Gudnason, and Arai.
(3) ClinicalTrials.gov Identifier: NCT01322568 (refer to archived version).
(4) This aspect of the study does not involve microarrays and therefore is not associated with a specific accession number or repository.

Conflict of interest: none declared.

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