Prevalence and Prognosis of Unrecognized Myocardial Infarction Determined by Cardiac Magnetic Resonance in Older Adults

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Context Unrecognized myocardial infarction (MI) is prognostically important. Electrocardiography (ECG) has limited sensitivity for detecting unrecognized MI (UMI).

Objective Determine prevalence and mortality risk for UMI detected by cardiac magnetic resonance (CMR) imaging or ECG among older individuals.

Design, Setting, and Participants ICELAND MI is a cohort substudy of the Age, Gene/Environment Susceptibility–Reykjavik Study (enrollment January 2004-January 2007) using ECG or CMR to detect UMI. From a community-dwelling cohort of older individuals in Iceland, data for 936 participants aged 67 to 93 years were analyzed, including 670 who were randomly selected and 266 with diabetes.

Main Outcome Measures Prevalence and mortality of MI through September 1, 2011. Results reported with 95% confidence limits and net reclassification improvement (NRI).

Results Of 936 participants, 91 had recognized MI (RMI) (9.7%; 95% CI, 8% to 12%), and 157 had UMI detected by CMR (17%; 95% CI, 14% to 19%), which was more prevalent than the 46 UMI detected by ECG (5%; 95% CI, 4% to 6%; $P<.001$). Participants with diabetes (n=337) had more UMI detected by CMR than by ECG (n=72; 21%; 95% CI, 17% to 26%, vs n=15; 4%; 95% CI, 2% to 7%; $P<.001$). Unrecognized MI by CMR was associated with atherosclerosis risk factors, coronary calcium, coronary revascularization, and peripheral vascular disease. Over a median of 6.4 years, 30 of 91 participants (33%; 95% CI, 23% to 43%) with RMI died, and 44 of 157 participants (28%; 95% CI, 21% to 35%) with UMI died, both higher rates than the 119 of 688 participants (17%; 95% CI, 15% to 20%) with no MI who died. Unrecognized MI by CMR improved risk stratification for mortality over RMI (NRI, 0.34; 95% CI, 0.16 to 0.53). Adjusting for age, sex, diabetes, and RMI, UMI by CMR remained associated with mortality (hazard ratio [HR], 1.45; 95% CI, 1.02 to 2.06, absolute risk increase [ARI], 8%) and significantly improved risk stratification for mortality (NRI, 0.16; 95% CI, 0.01 to 0.31), but UMI by ECG did not (HR, 0.88; 95% CI, 0.45 to 1.73; ARI, −2%; NRI, −0.05; 95% CI, −0.17 to 0.05). Compared with those with RMI, participants with UMI by CMR used cardiac medications such as statins less often (36%; 95% CI, 28% to 43%, or 56/157, vs 73%; 95% CI, 63% to 82%, or 66/91; $P<.001$).

Conclusions In a community-based cohort of older individuals, the prevalence of UMI by CMR was higher than the prevalence of RMI and was associated with increased mortality risk. In contrast, UMI by ECG prevalence was lower than that of RMI and was not associated with increased mortality risk.

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THE PREVALENCE AND PROGNOSIS of unrecognized myocardial infarction (MI) in older people with and without diabetes may be higher than previously suspected in population studies.[1-4] Advances in MI detection, such as cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE), are more sensitive than prior methods.[5] Ascertaining the prevalence of unrecognized MI (UMI) in these groups is relevant because age and diabetes increase the risks of coronary heart disease.[6] Pathologic studies[7] indicate that subclinical coronary plaque rupture occurs frequently, particularly in diabetic individuals, which may culminate in a high prevalence of UMI.

Several population studies[1-4] have described the prevalence of UMI based on electrocardiography (ECG), but ECG

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has significant limitations, such as limited sensitivity that varies with infarct location,[8] and Q waves may resolve over time.[9] Thus, the true prevalence of UMI may be significantly higher than appreciated in prior epidemiology studies. Cardiac magnetic resonance with LGE has been extensively validated for the detection of MI,[10] is more sensitive than single-photon emission computed tomography[11] or positron emission tomography,[12] and therefore is probably more sensitive than ECG. However, increased sensitivity is clinically important when the new test better identifies those at risk for adverse events.

The specific aim of this study was to compare the prevalence and prognosis of recognized and unrecognized MI diagnosed with CMR vs ECG in older diabetic and nondiabetic participants in ICELAND MI, a substudy of the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik). We hypothesized that UMI by CMR (1) would be more prevalent than UMI by ECG, in both diabetic and nondiabetic individuals; (2) would be associated with measures of atherosclerosis; and (3) would be significantly associated with increased mortality risk.

METHODS

ICELAND MI is an epidemiologic cohort study of diabetic and nondiabetic individuals. Participants were enrolled from January 2004 to January 2007, recruited from the AGES-Reykjavik Study (n=5764),[13] a randomly selected population-based cohort of men and women born between 1907 and 1935 who have been followed up in Iceland since 1967 by the Icelandic Heart Association. AGES-Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the Icelandic Heart Association and by the National Institute on Aging intramural institutional review board. Participants were eligible to participate in ICELAND MI if they provided written informed consent and were ineligible if they could not safely receive CMR scans (eg, they had implanted devices) or gadolinium contrast (eg, they had severe kidney disease). Participants were recruited from AGES-Reykjavik in 2 phases. The first phase involved random recruitment, and a second phase recruited all eligible and willing participants with diabetes.

Data Elements

Participants were characterized during 3 clinic visits.[13] Cardiac magnetic resonance studies occurred during a separate examination that included ECG. Participant surveillance has been ongoing since 1967 through the Icelandic Heart Association[13] and provided ascertainment of recognized MI (RMI).

Participants were defined as having an RMI when a history of MI was supported by hospital records or surveillance records.[13] Participants were defined as having a UMI by ECG when there was evidence of MI by ECG criteria (Minnesota codes 1.1.1-1.2.8).[1] Unrecognized MI by CMR meant there was no prior MI by hospital records or by surveillance records, and LGE involved the subendocardium in a coronary distribution. Other "atypical" patterns of LGE were specifically not designated as MI, a strategy that yields sensitivities and specificities greater than 90% for MI detection.[14-16] Cardiac magnetic resonance studies were interpreted by cardiologists blinded to clinical information.

Participants were further characterized with demographics, risk factors related to atherosclerosis, other comorbidities, biochemical measurements from blood, coronary calcium (Agatston scores), and ECG. Participants were classified as having diabetes according to standard criteria (fasting glucose ≥125 mg/dL; to convert to mmol/L, multiply by 0.0555)[17] or if they were already receiving treatment for diabetes. All-cause mortality was identified by review of hospital records as well as a national mortality index with authentication of all death certificates[13] through September 1, 2011.

Table 1. Baseline Characteristics of Participants

	All Participants (N = 936)
Age, median (IQR), y	76 (72-81)
Female sex, No. (%) [95% CI]	484 (52) [49-55]
BMI, median (IQR)[a]	27 (25-30)
CHD risk factors, No. (%) [95% CI]	
Hypertension	629 (67) [64-70]
Prior or current smoking	560 (60) [57-63]
Family history of MI	334 (36) [33-39]
Diabetes	337 (36) [33-39]
Hypercholesterolemia	421 (45) [42-48]
Coronary disease, No. (%) [95% CI][b]	
Prior MI	91 (10) [8-12]
Prior coronary revascularization	139 (15) [13-17]
Peripheral arterial disease, No. (%) [95% CI]	18 (2) [1-3]
Stroke, No. (%) [95% CI]	52 (6) [4-7]
Laboratory results, median (IQR)	
eGFR, mL/min per 1.73 m^2	69 (59-82)
Total cholesterol, mg/dL	208 (178-240)
HDL cholesterol, mg/dL	56 (46-68)
LDL cholesterol, mg/dL	128 (99-158)
Triglycerides, mg/dL	98 (75-135)
Coronary calcium score, Agatston[c]	361 (74-974)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction.
SI conversion factors: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; triglyceride to mmol/L, multiply by 0.0113.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Supported by hospital or surveillance records.
[c] Scores ranged from 0 to 7333. Coronary artery calcification occurs in atherosclerotic arteries and is absent in the normal vessel wall. Higher scores, measured by the Agatston method from computed tomographic scans, correlate with higher risks of coronary events.

CMR Studies

Cardiac magnetic resonance scans were performed on a 1.5-T scanner (GE Healthcare) using a 4-element cardiac phased array coil. Typical cine steady-state free precession (SSFP) scan parameters resulted in pixel dimensions of 1.8×2.1 mm, a slice thickness of 8 mm with a 3-mm gap, and 30 images per cycle. Standard long-axis and short-axis views were obtained to evaluate global and regional function.

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Table 2. Prevalence of Recognized and Unrecognized Myocardial Infarction by CMR or ECG Stratified by Diabetes Status[a]

	All Participants (N = 936)		Participants With Diabetes (n = 337)		Participants Without Diabetes (n = 599)	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
No MI	688	74 (71-76)	228	68 (63-73)	460	77 (73-80)
Clinically recognized MI	91	10 (8-12)	37	11 (8-14)	54	9 (7-11)
Unrecognized MI by ECG	46	5 (4-6)	15	4 (2-7)	31	5 (3-7)
Unrecognized MI by CMR	157	17 (14-19)	72	21 (17-26)	85	14 (11-17)
Cumulative MI by ECG	137	15 (12-17)	52	15 (12-19)	85	14 (11-17)
Cumulative MI by CMR	248	27 (24-29)	109	32 (27-37)	139	23 (20-27)

Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiography; MI, myocardial infarction.
[a] Unrecognized MI by CMR was observed roughly twice as often as recognized MI. The prevalence of MI with the addition of ECG was significantly higher than the prevalence without ECG but still significantly less than the increased prevalence with the addition of CMR ($P<.01$ for both).

The presence of MI was evaluated with a prospective, ECG gated, segmented, phase-sensitive gradient echo inversion recovery sequence approximately 6 to 25 minutes after 0.1-mmoL/kg intravenous gadolinium (Magnevist, Berlex).[18] Late gadolinium enhancement was designated MI by consensus of cardiologists experienced in CMR.

Statistical Analysis

Results are presented with 95% confidence intervals. We compared categorical variables with the χ^2 or Fisher test and continuous variables with the Wilcoxon rank-sum test. McNemar statistic was used to test whether CMR was more likely to detect UMI than ECG. We compared survival curve strata with the log-rank test. Tests for trend used χ^2 tests for categorical variables, linear regression for adjusted log coronary artery calcium (CAC) scores, and Kruskal Wallis for data that were not normally distributed.

Binary response variables were further analyzed by Cox regression survival analysis, and continuous variables were analyzed by linear regression. Multivariable Cox models adjusted for variation in key baseline characteristics included in prior epidemiologic studies using ECG: age, sex, diabetes, RMI, and finally UMI by CMR or UMI by ECG. Proportional hazards assumptions were verified by Schoenfeld residuals and time interaction terms. Absolute risk increases were calculated by measuring the survival rate difference before and after exponentiating the 7-year Kaplan-Meier survival rate in the reference group to the power of the adjusted hazard ratio (HR) in the comparison group. We used the integrated discrimination index (IDI) and net reclassification index (NRI) to evaluate the added predictive ability of survival models with the introduction of the UMI by CMR variable.[19,20]

Follow-up was enhanced by hospital record information, a national mortality index with authentication of all death certificates, a minimum data set for nursing home patients, and a minimum data set for home-care patients.[13] Coronary artery calcium was analyzed on the natural logarithm scale, ln(CAC+1). Two-sided *P* values less than .05 were considered significant. We used SAS version 9.2 (SAS Institute) to analyze the data.

RESULTS

For phase 1, 839 individuals were invited and 702 enrolled. In phase 2, 421 participants with diabetes were invited and 290 people enrolled (1005 total). Thirty-five participants declined CMR. Of those who underwent CMR (n=970), 34 participants had nondiagnostic CMR scans due to arrhythmia or inability to hold breath (n=14), claustrophobia (n=7), inability to gate cardiac images (n=3), technical issues with reconstruction and data transfer (n=9), or artifact from spinal implants (n=1). These participants were excluded, leaving a final cohort of 936 participants. Survivors were followed up for a median of 6.6 years (range, 4.6-7.7 years).

The median age was 76 years (interquartile range [IQR], 72-81 years; range, 68-94 years), and 52% (95% CI, 49%-55%) were women (484/936). Baseline characteristics are summarized in TABLE 1. ICELAND MI participants randomly selected in phase 1 had characteristics almost identical to the AGES-Reykjavik participants (eTable 1, available at http://www.jama.com).

Prevalence of MI Using CMR and ECG

A total of 91 of 936 participants (9.7%; 95% CI, 8%-12%) had RMI, and the prevalence of UMI by CMR was even higher (157/936; 17%; 95% CI, 14%-19%; $P<.001$), as shown in TABLE 2. Those with diabetes had a higher prevalence of UMI by CMR than those without diabetes (n=72; 21%; 95% CI, 17%-26%, vs n=85; 14%; 95% CI, 11%-17%, $P<.001$). Examples of CMR images are shown in FIGURE 1.

Cardiac magnetic resonance detected 157 UMI, which was more than the 46 UMI detected by ECG (prevalence by CMR, 17%; 95% CI, 14%-19%, vs ECG, 5%; 95% CI, 4%-6%, respectively, $P<.001$). There were 27 participants (3%; 95% CI, 2%-4%) with UMI by ECG who exhibited no MI on CMR, and there were 138 individuals (15%; 95% CI, 12%-17%) who had UMI by CMR yet did not meet criteria for

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UMI by ECG ($P<.001$). In the randomly sampled cohort (n=670), 61 participants (9%; 95% CI, 7%-11%) had RMI and 97 (14%; 95% CI, 12%-17%) had UMI by CMR whereas only 35 (5%; 95% CI, 4%-7%) had UMI by ECG, significantly less than UMI by CMR ($P<.001$).

Associations With Atherosclerosis and Diabetes

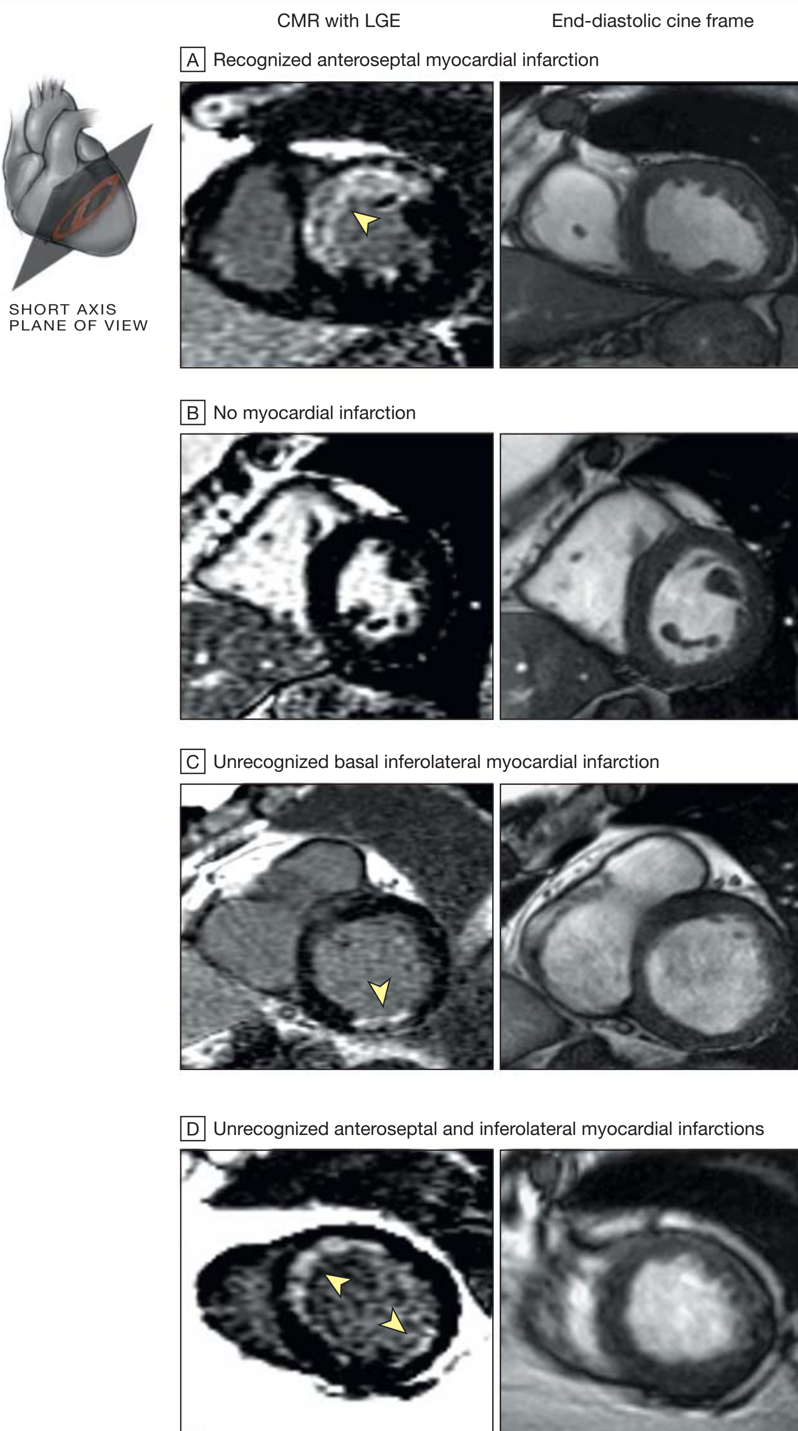
Coronary artery disease risk factors were more prevalent in participants with UMI compared with those with no MI. Compared with those without MI, participants with UMI were more frequently male, were slightly older, and had more hypertension and diabetes (TABLE 3). Similarly, those with UMI had more atherosclerosis with significantly higher coronary calcium scores than those without MI (Table 3). Overall, coronary calcium showed a significant graded relationship to the presence of MI, in which participants with UMI had coronary calcium scores intermediate between those without MI and those with clinically recognized MI (Table 3).

There was also a graded relationship between the likelihood of revascularization and MI status (Table 3). For 26 of 72 participants with diabetes (36%; 95% CI, 25%-47%) and 18 of 85 without diabetes (21%; 95% CI, 12%-30%) who had UMI had prior coronary revascularization. Excluding those with prior coronary revascularization (n=139), participants with and without diabetes still had high rates of UMI (46/273 or 17%; 95% CI, 12%-21%, vs 67/524 or 13%; 95% CI, 10%-16%, respectively). Thus, UMI was associated with atherosclerosis risk factors, coronary calcium, and treatment for atherosclerosis. Other characteristics of those with UMI by CMR are provided in Table 3.

Prognosis of RMI and UMI

Over a median follow-up of 6.4 years (IQR, 4.9-7.0 years), 30 of 91 participants with RMI died (33%; 95% CI, 23%-43%), and 44 of 157 with UMI by CMR died (28%; 95% CI, 21%-35%),

Figure 1. Representative Examples of Cardiac Magnetic Resonance Images Showing Recognized MI, No MI, and Unrecognized MI



All images are short-axis view, cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) on the left and end-diastolic cine frames on the right. A, Recognized myocardial infarction (MI) involving the typical left anterior descending artery distribution (arrowhead). On LGE images, an MI is brighter than remote or normal myocardium, which appears dark. B, Participant with no evidence of MI. The myocardium is uniformly dark ("nulled") on the LGE image. C, Unrecognized MI in the basal inferolateral wall (arrowhead). D, Two unrecognized MIs in different coronary territories in the same participant.

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which were both significantly higher rates than the 17% (95% CI, 15%-20%) with no MI who died (119/688). Both UMI by CMR and RMI had higher mortality compared with those without MI (HR, 1.81; 95% CI, 1.28 to 2.56; absolute risk increase, 13%, and HR, 2.20, 95% CI, 1.48 to 3.29, absolute risk increase, 19%, respectively). Unrecognized MI by CMR improved mortality risk stratification beyond RMI (category-free NRI, 0.34; 95% CI, 0.16 to 0.53). Unrecognized MI detected by ECG was not associated with higher mortality (HR, 0.95; 95% CI, 0.49 to 1.87; absolute risk increase, −1%). Unadjusted Kaplan-Meier survival curves for those without MI, those with UMI by CMR, and those with clinically recognized MI are shown in FIGURE 2. Five years after the CMR scan, the absolute mortality rates were 12% (95% CI, 9%-14%) for those without MI, 23% (95% CI, 16%-29%) with UMI by CMR, and 23% (95% CI, 17%-30%) in those with RMI. This culminated in approximately a 10% difference in absolute mortality rates between those with and without MI (eTable 2).

After adjusting for age, sex, diabetes, and RMI, UMI by CMR remained associated with mortality (HR, 1.45; 95% CI, 1.02 to 2.06; absolute risk increase, 8%), but UMI by ECG was not associated with mortality (HR, 0.88; 95% CI, 0.45 to 1.73; absolute risk increase, −2%). Similarly, UMI by CMR significantly improved the classification of those at risk for mortality (category-free NRI, 0.16; 95% CI, 0.01 to 0.31; $P=.04$), but UMI by ECG did not (NRI, −0.05; 95% CI, −0.17 to 0.05). Finally, UMI by CMR significantly improved mortality risk stratification (absolute IDI, 0.008; 95% CI, 0.004 to 0.013; $P<.001$), but UMI by ECG did not improve mortality risk stratification (IDI; 0.000; 95% CI, −0.001 to 0.001; $P=.71$).

Table 3. Associations of Recognized MI and Unrecognized MI Detected by CMR With Diabetes or Atherosclerosis

	No MI (n = 688)	Unrecognized MI (n = 157)	Recognized MI (n = 91)	*P* Value for Trend
Age, median (IQR), y	76 (72-80)	77 (74-83)	78 (74-82)	<.001
Women, No. (%) [95% CI]	395 (57) [54-61]	57 (36) [29-44][a]	32 (35) [25-45]	<.001
BMI, median (IQR)[b]	27 (25-30)	28 (25-30)	27 (24-31)	.80
CHD risk factors, No. (%) [95% CI]				
Hypertension	422 (61) [58-65]	124 (79) [73-85][a,c]	83 (91) [85-97]	<.001
Prior or current smoking	391 (58) [54-61]	98 (62) [55-70]	65 (71) [62-81]	.03
Family history of MI	237 (34) [31-38]	56 (36) [28-43]	41 (45) [35-55]	.14
Diabetes	228 (33) [30-37]	72 (46) [38-54][a]	37 (41) [31-51]	.007
Hypercholesterolemia	297 (43) [39-47]	72 (46) [38-54]	52 (57) [47-67]	.04
History of atherosclerosis, No. (%) [95% CI]				
Prior coronary revascularization	42 (6) [4-8]	44 (28) [21-35][a,c]	53 (58) [48-68]	<.001
Peripheral arterial disease	8 (1) [0-2]	6 (4) [1-7][a]	4 (4) [0-9]	.02
Stroke	33 (5) [3-6]	11 (7) [3-11]	8 (9) [3-15]	.20
Laboratory results, median (IQR)				
eGFR, mL/min per 1.73 m^2	70 (59-82)	68 (58-81)	64 (53-74)	.004
Total cholesterol, mg/dL	216 (185-243)	201 (170-239)[a,c]	178 (154-205)	<.001
HDL cholesterol, mg/dL	58 (47-69)	53 (45-63)[a]	51 (42-59)	<.001
LDL cholesterol, mg/dL	134 (108-162)	120 (91-157)[a,c]	98 (77-128)	<.001
Triglycerides, mg/dL	95 (73-132)	108 (79-148)[a]	104 (73-145)	.008
Coronary calcium score, Agatston[d]	227 (50-693)	792 (263-1713)[a,c]	1133 (654-2159)	<.001
Medications, No. (%) [95% CI]				
Aspirin	215 (31) [28-35]	81 (52) [44-59][a,c]	74 (81) [73-89]	<.001
β-Blocker	237 (34) [31-38]	70 (45) [37-52][a,c]	70 (77) [68-86]	<.001
Statins	153 (22) [20-25]	56 (36) [28-43][a,c]	66 (73) [63-82]	<.001
ACE inhibitors or ARBs	132 (19) [16-22]	42 (27) [20-34][a]	26 (29) [19-38]	.008
CMR characteristics, median (IQR)				
Ejection fraction %	63 (58-67)	60 (51-65)[a,c]	53 (42-61)	<.001
End diastolic volume index, mL/m^2	98 (87-111)	109 (92-124)[a,c]	113 (96-147)	<.001
Left ventricular mass index, g/m^2	72 (62-83)	83 (70-95)[a]	83 (69-102)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; BMI, body mass index; CHD, coronary heart disease; CMR, cardiac magnetic resonance; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction.

SI conversion factors: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; triglyceride to mmol/L, multiply by 0.0113.

[a] Significantly different compared with individuals without MI ($P<.05$). For coronary calcium, these differences persisted even after adjusting for age and sex.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Significantly different compared with those with recognized MI ($P<.05$). For coronary calcium, these differences persisted even after adjusting for age and sex.

[d] Scores ranged from 0 to 7333. Coronary artery calcification occurs in atherosclerotic arteries and is absent in the normal vessel wall. Higher scores, measured by the Agatston method from computed tomographic scans, correlate with higher risks of coronary events.

Treatment Differences

We observed more use of aspirin, β-blocker, and statin medications in those with UMI by CMR compared with those without MI. Yet the use of cardiac medications was significantly less in those with UMI compared with those with RMI (Table 3). Roughly half of those with UMI were taking aspirin, whereas less than half were taking statins or β-blockers.

COMMENT

Using CMR with a conservative interpretation scheme to detect MI in a cohort of community-dwelling older people, we found a high overall prevalence of UMI. More participants had UMI (17%) than RMI (9.7%), resulting in a much higher fraction of the population being identified as having an MI (26%). Individuals with diabetes had a particularly high prevalence

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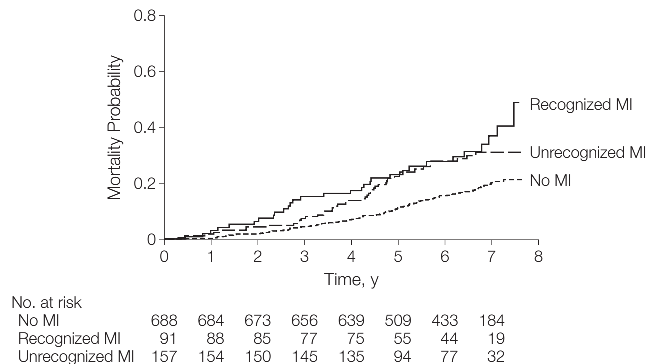
of UMI (21%), underscoring the designation of diabetes as a coronary risk equivalent,[6] but the pattern of more UMI than RMI was also true in those without diabetes.

Participants with UMI by CMR had higher coronary calcium, a higher prevalence of atherosclerotic disease, and a higher prevalence of traditional risk factors compared with those with no MI. Cardiac magnetic resonance was more sensitive than ECG in detecting UMI. Unrecognized MI detected by CMR was associated with subsequent mortality over 6 to 7 years, but UMI detected by ECG was not. Compared with those with RMI, participants with UMI by CMR received fewer prescriptions for medications used to prevent cardiovascular events. Considering the prevalence of UMI (17%) was higher than the prevalence of RMI (10%), many people might conceivably benefit from more intensive preventive therapy after UMI, but this hypothesis remains untested.

Several factors may contribute to the high prevalence of UMI. First, subclinical coronary plaque rupture occurs frequently, particularly in diabetic individuals.[21] Cardiac magnetic resonance may detect the myocardial sequelae of coronary plaque rupture or coronary plaque erosion[21] that either spontaneously reperfused or were nonocclusive. Second, symptom variation in acute MI[22] may lead patients or their clinicians to attribute MI symptoms to noncardiac causes. Third, given their propensity to be clinically detected, RMI may be more severe than UMI and impart greater lethality.[23,24] Survivor bias may also have increased the proportion of those with UMI in this study, but survivors are the only people eligible for post-MI secondary prevention.

The high prevalence of UMI highlights the advantages of using CMR for detection in epidemiology studies. Although the prevalence of UMI by ECG was similar to that in prior population studies,[1-4] ECG was much less sensitive for detecting UMI than CMR. Prior population studies probably underestimate the prevalence of MI and particularly UMI because they relied on ECG for detection. The mortality risk associated with UMI by ECG is less than previous reports[1,3]; smaller sample size, survivor bias, and different health care practices may be factors.

Figure 2. Mortality Curves According to Myocardial Infarction Status



The mortality was similar ($P=.40$) between recognized and unrecognized myocardial infarction (MI), and the mortality was significantly worse ($P<.001$) for those with unrecognized MI vs those without MI based on the log-rank test.

The increased mortality risk associated with UMI detected by CMR in a community-based cohort of older individuals is an important finding of this study, since we document a high prevalence of UMI. In fact, we found that the majority of all MIs were clinically unrecognized, suggesting a significant public health burden. This association between prevalent UMI and mortality is novel, because prior epidemiology studies relying on ECG data indicated that a minority of MIs are clinically unrecognized.[1-4] Our study is also the first epidemiology study, to our knowledge, to associate coronary calcium with evident MI on CMR LGE images. Although another smaller study using LGE in 248 individuals also reported that most MIs were unrecognized, the study sampled only 75-year-old individuals and could not determine the association with mortality controlling for age.[25] Unrecognized MI appears to represent an intermediate phenotype in the evolution of coronary heart disease, given its graded association with atherosclerosis risk factors, coronary calcium, overt atherosclerosis, and subsequent mortality risk.

Other studies have associated UMI identified by CMR with adverse outcomes, but these studies were not community-based epidemiology studies; instead, they were conducted in referral populations with higher baseline risk and inherent biases.[24,26,27] The relative risk of UMI may be higher in these studies due to referral biases not present in our community-based population study. Nonetheless, the current study indicates that the adverse outcomes associated with UMI extend to the community. Our study also indicates that CMR is more robust at detecting MI and more strongly associated with mortality compared with ECG—an observation with important implications for future epidemiology studies of UMI.

Several lines of evidence establish that the designation of UMI represents true MI.[10,14,16,28,29] First, CMR scans were interpreted conservatively. Specifically, atypical patterns of enhancement seen with conditions unrelated to coronary disease were not designated as MI. Second, the prevalence of risk factors for coronary heart disease or established atherosclerotic disease documented multiple associations of UMI by CMR with atherosclerosis. Kim et al[27] have also shown associations between coronary disease and UMI. Furthermore, the association between UMI de-

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tected by LGE and mortality also supports the diagnosis of MI.

This investigation also suggests limitations in current prevention strategies. Herein we report a burden of MI in community-dwelling older individuals that is higher than previously appreciated. The burden of UMI was higher than the total burden of recognized MI, and prescription of cardioprotective medications was less than for participants with RMI. The high prevalence of MI specifically in individuals with diabetes confirms their increased vulnerability. Less than one-third of those with UMI by CMR had prior revascularization to establish coronary disease and trigger secondary prevention strategies. Detection of UMI by CMR may provide an opportunity to optimize treatment for these vulnerable individuals, but further study is needed to assess this.

The AGES-Reykjavik cohort provides results that are most applicable to white participants and may not extend to other ethnicities. The sensitivity of CMR for detecting chronic MI using a 0.1-mmoL/kg gadolinium contrast dose in our study may be lower compared with higher doses.[16] However, if our study actually had low sensitivity, then the true prevalence of MI would be higher. Mitigating the issue of contrast dose, the phase-sensitive LGE[18] method used in this study has better signal-to-noise ratio at low-contrast doses than conventional LGE methods. In the minority of participants with both UMI and prior coronary revascularization, we could not ascertain whether UMI occurred independently or as a clinically unappreciated consequence of revascularization. Nonetheless, revascularization complications do not explain the high prevalence of UMI because the prevalence of UMI in participants with and without diabetes remained high even after excluding prior coronary revascularization. We also did not examine more subtle ECG changes that may be associated with MI. Risk adjustment was limited. This study was designed to demonstrate comparable prognoses between UMI and RMI; it was not powered to permit extensive risk adjustment for all baseline differences.

CONCLUSIONS

Older individuals in the community had a high prevalence of MI, especially those with diabetes. Most MIs were unrecognized, despite associations with atherosclerosis, risk factors, and health care advances. Cardiac magnetic resonance with LGE detected more UMI and was more strongly associated with mortality than ECG. Unrecognized MI detected by CMR with LGE was associated with mortality similar to recognized MI. Participants with UMI received fewer cardiac medications than those with RMI.

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Experimentation must always be devised in view of a preconceived idea, no matter if the idea be not very clear nor very well-defined. As for noting the results of the experiment, . . . we must here, as always, observe without a preconceived idea.

——Claude Bernard (1813-1878)

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