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Long-Term Prognostic Implications of Previous Silent Myocardial Infarction in Patients Presenting With Acute Myocardial Infarction

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ABSTRACT

OBJECTIVES This study investigated the prevalence of silent myocardial infarction (MI) in patients presenting with first acute myocardial infarction (AMI), and its relation with mortality and major adverse cardiovascular events (MACE) at long-term follow-up.

BACKGROUND Up to 54% of MI occurs without apparent symptoms. The prevalence and long-term prognostic implications of previous silent MI in patients presenting with seemingly first AMI are unclear.

METHODS A 2-center observational longitudinal study was performed in 392 patients presenting with first AMI between 2003 and 2013, who underwent late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) examination within 14 days post-AMI. Silent MI was assessed on LGE-CMR images by identifying regions of hyperenhancement with an ischemic distribution pattern in other territories than the AMI. Mortality and MACE (all-cause death, reinfarction, coronary artery bypass grafting, and ischemic stroke) were assessed at 6.8 ± 2.9 years follow-up.

RESULTS Thirty-two patients (8.2%) showed silent MI on LGE-CMR. Compared with patients without silent MI, mortality risk was higher in patients with silent MI (hazard ratio: 3.87; 95% confidence interval: 1.21 to 12.38; p = 0.023), as was risk of MACE (hazard ratio: 3.10; 95% confidence interval: 1.22 to 7.86; p = 0.017), both independent from clinical and infarction-related characteristics.

CONCLUSIONS Silent MI occurred in 8.2% of patients presenting with first AMI and was independently related to poorer long-term clinical outcome, with a more than 3-fold risk of mortality and MACE. Silent MI holds prognostic value over important traditional prognosticators in the setting of AMI, indicating that these patients represent a high-risk subgroup warranting clinical awareness. (J Am Coll Cardiol Img 2018;11:1773–81) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Because patients after acute myocardial infarction (AMI) are at risk for new events and premature death, secondary prevention is an essential part of patient care. To optimize secondary prevention in these patients, there is a need to identify high-risk subgroups (1,2). Previous work has suggested that patients with a previous unrecognized or silent myocardial infarction (MI) may represent a high-risk subgroup. Current knowledge of silent MI in the setting of AMI is, however, incomplete.

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CAD = coronary artery disease

CI = confidence interval

CMR = cardiac magnetic resonance

ECG = electrocardiogram

HR = hazard ratio

LGE = late gadolinium enhancement

LV = left ventricular

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

STEMI = ST-segment elevation myocardial infarction

Silent MI is usually discovered by routine electrocardiogram (ECG) examination. Because of scar tissue in the infarcted myocardium, Q waves may be seen on the ECG. Although the ECG seems to be an appropriate screening tool in the general population, smaller infarctions can be missed and not all patients develop Q waves after infarction, thereby limiting the sensitivity of the ECG (3). The preferred method for silent MI detection is late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR), which provides the unique possibility of tissue characterization. LGE-CMR is considered the best available technique for noninvasive assessment of myocardial scar tissue following MI (4), yet this technique has never been used to investigate the prevalence and prognostic implications of previous silent MI in patients presenting with AMI.

SEE PAGE 1782

Silent MI constitutes up to 54% of all MIs in the general population and more than 60% in the elderly population older than 60 years, with increasing prevalence in presence of cardiovascular risk factors (3,5). Reported prevalence of silent MI ranges from 0.5% to 8.0% in the general population and rises up to 27% in patients with suspected coronary artery disease (CAD) (5–8). In these populations the presence of silent MI has been linked to poorer prognosis (3,7–9). In the setting of AMI only 1 prior study has investigated silent MI. In this study, 7.3% of patients had silent MI detected by Q waves on the ECG, and silent MI was associated with a higher risk of major adverse cardiovascular events (MACE), but not mortality, at short-term follow-up of 90 days (10).

In addition to the lack of long-term data and current knowledge largely being based on a suboptimal detection method, it is unclear whether silent MI holds prognostic value over important traditional prognosticators (i.e., left ventricular [LV] ejection fraction and [acute] infarct size). Therefore, the current study assessed, for the first time, the prevalence of silent MI by LGE-CMR in patients presenting with AMI, and its relationship with mortality and MACE after 2 to 12 years follow-up. In addition, the diagnostic accuracy of the ECG for silent MI detection was assessed.

METHODS

In this observational longitudinal study, 405 patients presenting with AMI between 2003 and 2013, without a history of prior MI, who underwent LGE-CMR within 14 days of AMI, were identified from existing databases of the VU University Medical Center and Maastricht University Medical Center in the Netherlands. These databases consisted of prospectively enrolled first AMI patients who provided informed consent for follow-up during the index hospitalization. Of the 405 eligible patients, 392 were included in this study. Reasons for exclusion were insufficient quality or incompleteness of LGE-CMR images (i.e., because of breathing artifacts or premature termination of CMR examination caused by claustrophobia).

CMR PROTOCOL. Patients underwent CMR within 14 days (5.5 ± 3.2 and 5.4 ± 2.9 days for patients with and without silent MI, respectively) after presenting with AMI, using a 1.5-T clinical MR scanner (Sonata or Avanto, Siemens, Erlangen, Germany; or Intera, Philips Medical Systems, Best, the Netherlands). In summary, balanced steady-state free precession imaging was performed in standard long-axis and short-axis views covering the whole left ventricle to measure LV dimensions and calculate LV ejection fraction. Typical parameters were: in-plane resolution, 1.6 × 2.0 mm; slice thickness/slice gap, 5/5 mm, 6/4 mm; flip angle, 40° to 75°; temporal resolution, 35 to 50 ms; repetition time/echo time, 3.4/1.7. LGE imaging was performed using an inversion recovery gradient-echo sequence 10 to 15 min after administration of 0.2 mmol/kg gadolinium-based contrast agent (Magnevist, Schering, Berlin, Germany or Dotarem, Guerbet, Roissy, CdG, France) in standard long and short axis orientations covering the whole left ventricle. Typical parameters were: in-plane resolution, 1.5 × 1.5 mm; slice thickness, 5 to 8 mm; repetition time, 3.9 to 9.6 ms; echo time, 2.4 to 4.4 ms; flip angle, 25°; inversion time, 250 to 350 ms nulled to normal myocardium. The presence of MI was assessed on the LGE-CMR images by identifying regions of contrast enhancement with an ischemic distribution pattern (i.e., subendocardial or transmural hyperenhancement). Silent MI was defined as ischemic contrast enhancement in other areas than the current AMI. In case of multiple areas of infarction, the coronary angiography results were used to support identification of the area corresponding to the culprit artery of AMI. Infarct size of both acute and silent MI was measured using the full width at one-half maximum method. Microvascular obstruction was defined as presence of a hypoenhanced core within hyperenhanced infarcted myocardium. Areas of microvascular obstruction were included in the total acute infarct size. All CMR analyses were performed by a trained researcher (R.P.A.) and controlled by an experienced reader (R.N.), all blinded to clinical

data except the culprit artery of the acute infarction by coronary angiography. All CMR images were analyzed using dedicated off-line software (QMassMR version 7.6, Medis, Leiden, the Netherlands).

ELECTROCARDIOGRAM. ECGs from 388 patients (99%) were retrieved from the electronic patient records. The presence of Q waves was assessed on the presenting ECG (standard 12-lead), following the European Society of Cardiology/American College of Cardiology expert consensus document (11). Q waves outside the area of acute infarction were considered indicative of silent MI. ECGs were analyzed by a trained researcher (A.Z.) and controlled by an experienced reader (C.P.A.), blinded to clinical and CMR data.

CLINICAL CHARACTERISTICS. Demographic characteristics, cardiovascular risk profile, cardiovascular medical history, medical therapy before hospitalization (i.e., beta blocker, acetylsalicylic acid, $P2Y_{12}$-inhibitor, statin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and calcium blocker therapy), and infarct-related and treatment-related characteristics were identified from the electronic patient record systems. Type of AMI was either ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Hemodynamic support during hospitalization was defined as a need for positive inotropic medication, mechanical support (i.e., intra-aortic balloon pump or ventricular assist device), or temporary pacing. Vessel disease was categorized as 1-, 2-, or 3-vessel disease based on the number of coronary arteries with a stenosis of >50% on coronary angiography. Reperfusion strategy was categorized as direct, deferred, or none. Direct reperfusion was defined as primary percutaneous coronary intervention, plain old balloon angioplasty, thrombolysis, or coronary artery bypass grafting performed directly after acute coronary angiography on hospitalization. Deferred reperfusion was defined as percutaneous coronary intervention, plain old balloon angioplasty, or coronary artery bypass grafting performed after nonacute coronary angiography during hospitalization.

CLINICAL OUTCOME. All-cause mortality data were retrieved from the municipal civil registry (Gemeentelijke Basis Administratie) for all patients. MACE was a composite endpoint including all-cause death, reinfarction, coronary artery bypass grafting, and ischemic stroke. In case of multiple MACE endpoints in 1 patient, the date of the first event was used for event-free survival analysis (death > reinfarction > ischemic stroke > coronary artery bypass grafting). MACE data other than death were retrieved via structured telephone interviews with patients, consisting of the following items: hospitalization for AMI, coronary artery bypass grafting, and/or ischemic stroke; and if yes, the date of hospitalization. The questionnaire was sent to all patients via mail at least

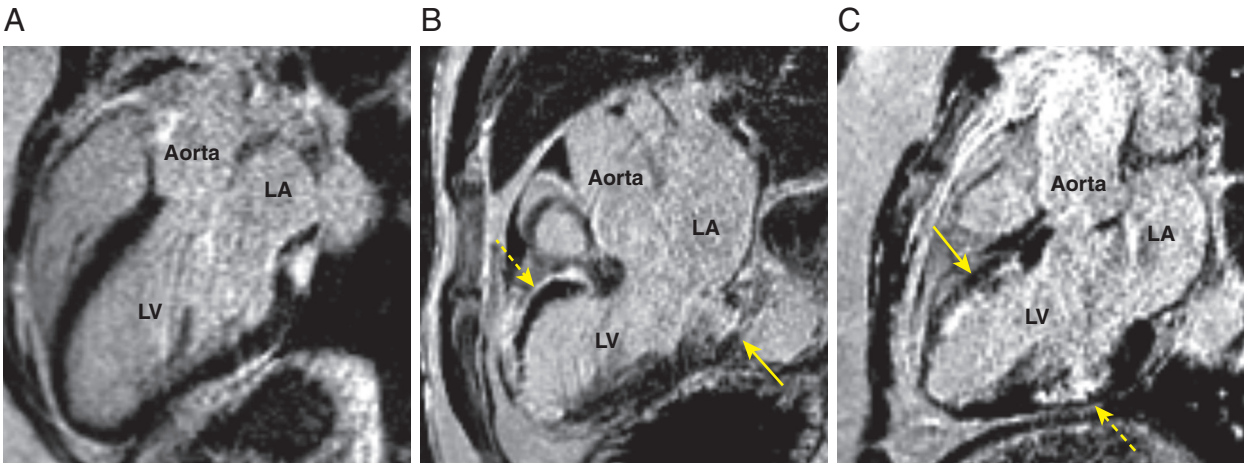
TABLE 1 Clinical Characteristics

	All Patients (N = 392)	AMI With Silent MI (n = 32)	AMI Without Silent MI (n = 360)	p Value
Age, yrs	58.3 ± 11.2	61.8 ± 9.4	58.0 ± 11.3	0.071
Male	301 (77)	24 (75)	277 (77)	0.83
Hypertension	118 (31)	13 (42)	105 (30)	0.16
Diabetes mellitus	24 (6)	2 (7)	22 (6)	>0.99
Hypercholesterolemia	71 (20)	7 (28)	64 (20)	0.31
Smoking	249 (69)	21 (81)	228 (68)	0.27
Family history of CAD	145 (40)	9 (38)	136 (41)	0.83
History of PCI	7 (2)	2 (6)	5 (1)	0.11
History of coronary artery bypass grafting	5 (1)	1 (3)	4 (1)	0.35
History of stroke	3 (1)	0 (0)	3 (1)	>0.99
History of transient ischemic attack	11 (3)	1 (3)	10 (3)	>0.99
History of peripheral arterial disease	18 (5)	0 (0)	18 (6)	0.39
Pre-hospital medication	110 (30)	15 (48)	95 (28)	0.021
Beta blocker	40 (11)	8 (26)	32 (10)	0.012
Acetylsalicylic acid	28 (8)	5 (16)	23 (7)	0.077
$P2Y_{12}$-inhibitor	5 (1)	1 (3)	4 (1)	0.36
Statin	43 (12)	8 (27)	35 (11)	0.016
ACE inhibitor/ARB	44 (12)	7 (23)	37 (11)	0.073
Calcium channel antagonist	22 (6)	5 (17)	17 (5)	0.026
STEMI	362 (95)	27 (84)	335 (95)	0.023
Pre-angina pectoris	157 (49)	15 (48)	142 (49)	>0.99
Hemodynamic support	15 (4)	0 (0)	15 (5)	0.38
Infarct-related artery				0.95
Left anterior descending	162 (50)	14 (54)	148 (49)	
Circumflex	33 (10)	2 (8)	31 (10)	
Right coronary artery	132 (40)	10 (39)	122 (41)	
Vessel disease				0.34
1-vessel disease	205 (57)	13 (48)	192 (58)	
2-vessel disease	94 (26)	7 (26)	87 (26)	
3-vessel disease	58 (16)	7 (26)	51 (16)	
Treatment of infarction				0.002
Direct (acute) reperfusion	342 (87)	22 (69)	320 (89)	
Deferred reperfusion	19 (5)	6 (19)	13 (4)	
No reperfusion	31 (8)	4 (13)	27 (8)	
LV end-diastolic volume, ml	180 (154–208)	185 (145–277)	180 (155–204)	0.60
LV end-systolic volume, ml	89 (71–113)	88 (73–147)	89 (71–112)	0.23
LV ejection fraction, %	49 ± 10	44 ± 14	49 ± 9	0.006
LV mass, g	118 ± 31	126 ± 41	117 ± 30	0.16
Infarct size of acute infarction, g	21.7 (10.1–34.4)	23.8 (8.5–6.3)	22.0 (10.5–34.1)	0.71
Infarct size of silent infarction, g	5.1 (1.4–11.5)	5.1 (1.4–11.5)	NA	NA
Microvascular obstruction	192 (50)	17 (55)	175 (50)	0.71
Follow-up duration, yrs	6.8 ± 2.9	5.9 ± 2.6	6.9 ± 2.9	0.054

Values are mean ± SD, n (%) or median (interquartile range).

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CAD = coronary artery disease; LV = left ventricular; MI = myocardial infarction; NA = not applicable; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

FIGURE 1 Examples of Silent MI



Late gadolinium enhancement cardiac magnetic resonance images in 3-chamber view showing the aorta, left atrium, left ventricle, and anteroseptal and inferolateral myocardium in **(A)** a patient without MI; **(B)** a patient with transmural anteroseptal acute MI **(dotted arrow)**, with a large area of microvascular obstruction as shown by the hypointense core within the hyperenhanced area, and transmural basal inferolateral silent MI with myocardial wall thinning **(arrow)**; and **(C)** a patient with inferolateral acute MI **(dotted arrow)** and subendocardial anteroseptal silent MI **(arrow)**. LA = left atrium; LV = left ventricle; MI = myocardial infarction.

1 month before the telephone interview, to reduce recall bias. Of the surviving patients, 320 (92%) were reached by telephone for the MACE questionnaire. All follow-up data were obtained in the period from October to December 2015, resulting in mean follow-up duration of 6.8 ± 2.9 years.

STATISTICAL METHODS. Continuous variables are presented as mean ± SD when normally distributed, or as median (interquartile range) when not-normally distributed. Categorical variables are presented as number and percentage. We compared continuous variables between patients with and without silent MI using Student's *t*-test and Mann-Whitney *U* test as appropriate. Categorical variables were compared using Fisher exact test. Diagnostic accuracy parameters of ECG for silent MI detection (i.e., sensitivity, specificity, positive and negative predictive value) were calculated by comparing with silent MI by LGE-CMR as reference technique, and McNemar test was used to compare the performance of these 2 techniques. To investigate clinical outcome in patients with silent MI compared with patients without silent MI, Cox proportional hazards analyses were performed. First, univariable Cox regression analyses were performed for silent MI with all-cause mortality and MACE (outcome measures in separate models). Subsequently we adjusted for age, sex, study site, pre-hospital medication (yes vs. no), type of AMI (STEMI vs. non-STEMI), number of vessel disease, reperfusion strategy (categorized into direct, deferred, or none), LV ejection fraction, total infarct size (sum of acute and silent MI), and microvascular obstruction. Additionally, risk of mortality and MACE in relation to Q waves by ECG was investigated with univariable Cox regression analyses. Proportional hazard assumptions were verified by Schoenfeld residuals and time interaction terms. Values of $p < 0.05$ were considered statistically significant.

TABLE 2 Long-Term Clinical Outcome

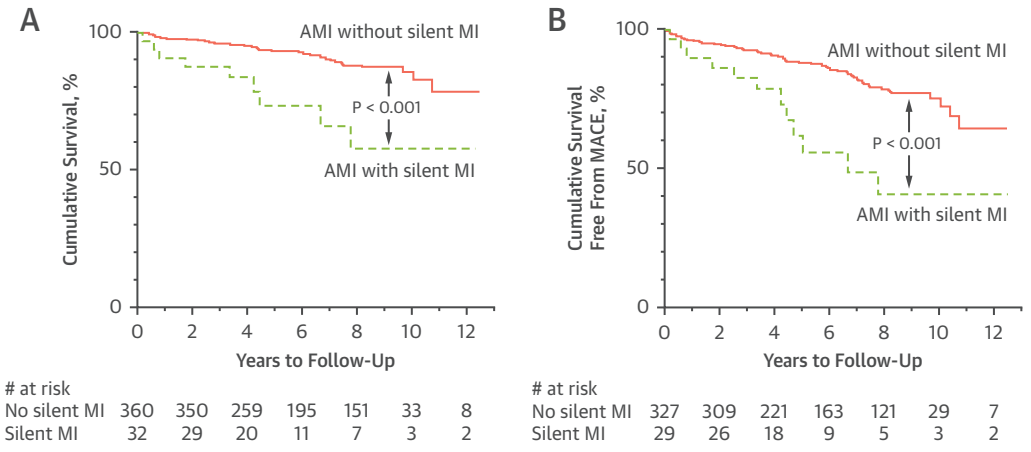
	AMI With Silent MI (n = 32)	AMI Without Silent MI (n = 360)	p Value
MACE	12 (41.4)	58 (17.7)	0.002
Death	9 (28.1)	36 (10.0)	0.002
Reinfarction	2 (6.3)	10 (2.8)	0.155
Ischemic stroke	1 (3.1)	5 (1.4)	0.319
Coronary artery bypass grafting	0 (0.0)	7 (1.9)	0.476

Values are n (%).
MACE = major adverse cardiovascular event(s); other abbreviations as in Table 1.

RESULTS

Table 1 shows the clinical characteristics of the study population. Patients were on average 58.3 ± 11.2 years of age and 77% were men. Of the 392 patients, 32 patients (8.2%) showed silent MI. Figure 1 shows

FIGURE 2 Long-Term Clinical Outcome of Silent MI by Late Gadolinium Enhancement Cardiac Magnetic Resonance



Kaplan-Meier curves showing **(A)** increased mortality and **(B)** increased MACE (composite endpoint of all-cause death, reinfarction, coronary artery bypass graft, and ischemic stroke) in patients with silent MI compared with those without silent MI by late gadolinium enhancement cardiac magnetic resonance. AMI = acute myocardial infarction; other abbreviation as in Figure 1.

a typical example of silent MI on the LGE-CMR images. Patients with silent MI tended to be older than patients without silent MI, although not statistically significant (62 ± 9 vs. 58 ± 11 years of age; p = 0.071). Patients with silent MI used medication before hospitalization more often (48% vs. 28%; p = 0.021), presented with STEMI less often (84% vs. 95%; p = 0.023), and had deferred or no reperfusion more often (19% vs. 4% and 13% vs. 8%, respectively; overall p = 0.002). Cardiovascular risk factors, medical history, infarct-related artery, and number of coronary vessel disease were comparable between the groups.

Although LV end-diastolic and end-systolic volumes did not differ significantly between patients with and without silent MI, LV ejection fraction was significantly lower in those with silent MI (44 ± 14% vs. 49 ± 9%; p = 0.006). Infarct size of AMI was comparable for patients with and without silent MI (median 23.8 g [interquartile range: 8.5 to 46.3 g] vs. 22.0 g [interquartile range: 10.5 to 34.1 g]; p = 0.71). Infarct size of silent MI was 5.1 g (interquartile range: 1.4 to 11.5 g). Occurrence of microvascular obstruction was similar between patients with and without silent MI (55% vs. 50%; p = 0.71).

SILENT MI AND CLINICAL OUTCOME. Occurrence of all-cause death and MACE is shown in Table 2. Nine (28.1%) patients with silent MI died during follow-up, compared with 36 (10.0%) patients without silent MI (Figure 2). Univariable Cox proportional hazards analysis showed a higher risk of death in patients with silent MI compared with those without silent MI (hazard ratio [HR]: 3.69; 95% confidence interval [CI]: 1.77 to 7.67; p < 0.001). Silent MI remained significantly associated with all-cause death in multivariable analysis, showing an HR of 3.87 (95% CI: 1.21 to 12.38; p = 0.023) adjusted for age, sex, study site, pre-hospital medication, type of AMI, number of vessel disease, reperfusion strategy, LV ejection fraction, total infarct size, and microvascular obstruction (Table 3).

During follow-up 12 (41.4%) patients with silent MI experienced a MACE endpoint compared with 58 (17.7%) patients without silent MI (Figure 2). In addition to increased all-cause death as mentioned previously, patients with silent MI showed more

TABLE 3 Univariable and Multivariable Cox Regression Analyses of Silent Myocardial Infarction and Long-Term Clinical Outcome

	Univariable		Multivariable*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Death	3.69 (1.77–7.67)	<0.001	3.87 (1.21–12.38)	0.023
MACE (death, reinfarction, ischemic stroke, coronary artery bypass grafting)	3.05 (1.64–5.70)	<0.001	3.10 (1.22–7.86)	0.017

*Adjusted for age, sex, study site, pre-hospital medication, type of acute myocardial infarction (with or without ST-segment elevation), reperfusion strategy (direct, deferred, or none), number of vessel disease, left ventricular ejection fraction, total infarct size, and microvascular obstruction.

CI = confidence interval; HR = hazard ratio; other abbreviation as in Table 2.

TABLE 4 Diagnostic Accuracy of Q Waves by Electrocardiogram for Silent MI Detection

	Silent MI by LGE-CMR	No Silent MI by LGE-CMR	
Q waves present	3	8	Positive predictive value = 27%
Q waves absent	28	342	Negative predictive value = 92%
	Sensitivity = 9.7%	Specificity = 98%	

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance; other abbreviation as in Table 1.

frequent reinfarction (6.3% vs. 2.8%; p = 0.155) and ischemic stroke (3.1% vs. 1.4%; p = 0.319), although these differences were not statistically significant for individual endpoints. Coronary artery bypass grafting during follow-up was less frequent in patients with silent MI (0% vs. 1.9%; p = 0.476). Univariable Cox proportional hazards analysis showed a higher risk of MACE in patients with silent MI compared with patients without silent MI (HR: 3.05; 95% CI: 1.64 to 5.70; p < 0.001). This association remained statistically significant in multivariable analysis, showing an HR of 3.10 (95% CI: 1.22 to 7.86; p = 0.017) adjusted for age, sex, study site, pre-hospital medication, type of AMI, number of vessel disease, reperfusion strategy, LV ejection fraction, total infarct size, and microvascular obstruction.

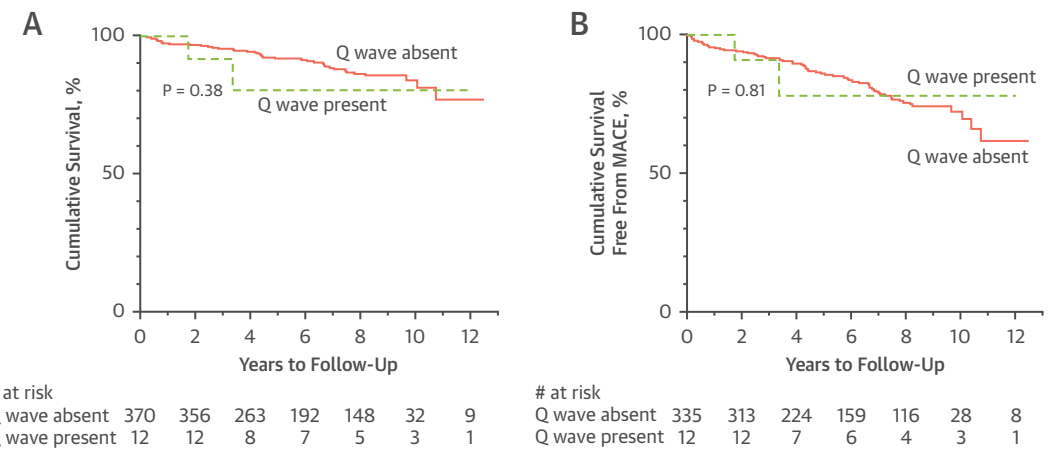
SILENT MI BY ECG VERSUS LGE-CMR. Seven ECGs were considered inconclusive because of arrhythmia, unclear culprit artery on the ECG, or right-sided lead placement, and were therefore excluded from analysis. Table 4 shows the detection of silent MI by ECG compared with LGE-CMR. Eleven patients (2.9%) showed silent MI by Q waves on the ECG, of whom 3 patients (27%) had silent MI by LGE-CMR. Among 370 patients without Q waves by ECG, 28 patients (7.6%) had silent MI by LGE-CMR. Diagnostic accuracy of ECG compared with LGE-CMR for silent MI detection was: sensitivity = 9.7%, specificity = 98%, positive predictive value = 27%, and negative predictive value = 92%. McNemar test showed a statistically significant difference between ECG and LGE-CMR for silent MI detection (2.9% vs. 8.2%; p = 0.002).

As shown in Figure 3, Q waves by ECG were not significantly associated with all-cause mortality and MACE in univariable Cox proportional hazards analyses, showing HRs of 1.88 (95% CI: 0.45 to 7.78; p = 0.38) and 1.19 (95% CI: 0.29 to 4.87; p = 0.81), respectively.

DISCUSSION

The main findings of our study are summarized as follows: 1) previous silent MI was found in 8.2% of patients presenting with first AMI; 2) silent MI by LGE-CMR was a strong, independent predictor for adverse long-term clinical outcome; and 3) the ECG has limited sensitivity for detection of silent MI and was not associated with long-term clinical outcome

FIGURE 3 Long-Term Clinical Outcome of Q Waves by Electrocardiogram



Kaplan-Meier curves showing similar risk of **(A)** mortality and **(B)** MACE (composite endpoint of all-cause death, reinfarction, coronary artery bypass graft, and ischemic stroke) in patients with and without Q waves by electrocardiogram. Abbreviation as in Figure 1.

in our study cohort. This is the first study in patients with AMI to investigate silent MI using LGE-CMR, and to assess its long-term prognostic implications.

Higher risk of mortality and/or MACE after silent MI has consistently been reported in different patient populations with varying follow-up duration (i.e., up to 11 years in the general population [3,9], up to 6 years in patients with stable CAD [7,8], and 90 days in patients with AMI [10]). Our study confirms these findings and extends the inferred prognostic implications to a longer follow-up period of up to 12 years, and a hard clinical endpoint (i.e., mortality). Moreover, the prognostic value of silent MI was proven not only to be independent from clinical characteristics, but also from important traditional prognosticators after AMI (i.e., LV ejection fraction, infarct size, and microvascular obstruction). This provides a crucial addition to the body of evidence for poorer clinical outcome in patients with silent MI, even in the setting of first AMI.

The prognostic value of silent MI may become useful in risk stratification to guide secondary prevention. Although silent MI is not a modifiable risk factor, the intensity of outpatient monitoring and pharmacologic cardioprotective treatment following AMI can be tailored to the individual patient. Patients with AMI and previous silent MI are a high-risk subgroup, in which the clinician may consider more strict monitoring and/or treatment. Other clinical implications might include a lower threshold for ischemia detection or coronary angiography if these patients present again with few or atypical symptoms or implantation of a cardioverter defibrillator if LV ejection fraction is around the 35% cutoff value.

In addition to relevance for clinical practice, the associated increase in mortality and MACE warrants consideration of silent MI in studies investigating prognosis or therapeutic interventions in AMI, because of the possible confounding effect. This should be feasible with relatively little effort, because the comprehensive assessment of infarct characteristics and LV function have already made LGE-CMR widely applied in these studies. Also, when follow-up LGE-CMR is performed, the occurrence of silent MI might be included in MACE endpoints.

In line with previous work in the general population and stable CAD patients (3,7), our study demonstrated suboptimal diagnostic accuracy for ECG-based silent MI detection in the setting of AMI. Factors complicating silent MI assessment by ECG include the relatively small infarct size of silent MIs; arrhythmias in the setting of AMI; and presence of Q waves related to the acute event, which may be difficult to differentiate from old Q waves because of natural variance in coronary artery anatomy. It should also be noted that previous silent MI in the same area as the acute infarction cannot be detected by LGE-CMR or ECG; this is inherent to this study population and perhaps silent MI is still underestimated in this patient population.

In addition to the added value of LGE-CMR in detecting silent MI, the value of LGE-CMR is reflected in the effect size for the relation of silent MI with mortality and MACE. In all previously mentioned studies, the reported increased risk of mortality and/or MACE was consistently larger when silent MI was assessed by LGE-CMR versus by ECG. A large population-based study showed a nonsignificant HR of 0.95 for mortality based on ECG versus a significant HR of 1.81 when silent MI was assessed by LGE-CMR in the same study (3). Likewise, in patients with stable CAD the reported HR for mortality and MACE increased from approximately 1.5 based on ECG to 11.4 in studies using LGE-CMR (7,8,12). In patients with AMI we found HRs of 3.87 and 3.10 for mortality and MACE, respectively, when using LGE-CMR, whereas nonsignificant HRs of 1.88 and 1.19 were found when using Q waves by ECG. A previous ECG-based study in patients with AMI found a nonsignificant HR of 1.44 for mortality and HR of 1.46 for MACE (10). This trend is likely a reflection of misclassification in both directions (i.e., false-positives and false-negatives) when using the ECG and underlines the importance of using LGE-CMR for silent MI assessment.

Finally, several questions remain, especially regarding pathophysiology of silent MI and the mechanism leading to poorer prognosis. Although previous studies showed traditional cardiovascular risk factors, especially diabetes mellitus, to be associated with occurrence of silent MI, this was not apparent in our study (3,6). This may be a result of selecting those patients who at some point in time do present with clinical AMI. Patients who experience only silent MIs remain invisible in this regard. Also, the overall prevalence of diabetes mellitus was quite low (6%) in this cohort of first AMI patients. Silent MI did occur more often in patients with non-STEMI-type infarction, with less frequent need for direct reperfusion. Hypothetically, this might point to a different pathophysiology or manifestation of atherosclerotic disease in these patients. This is in

line with previous work demonstrating that silent MI is not associated with significant atherosclerosis on whole body MR angiography, whereas a history of recognized MI was (13). Regarding the relation of silent MI with poorer prognosis, silent MIs by definition have not been treated appropriately, hence cumulative myocardial damage is likely larger in those with previous silent MI. This results in more functionally impaired myocardium and more fibrotic scar tissue, thereby possibly increasing the substrate for adverse LV remodeling and sudden cardiac death. The lower LV ejection fraction in the acute phase after AMI in patients with silent MI in our study supports this hypothesis. Future studies should investigate the development of LV dilatation and functional impairment over time with serial cardiac imaging, preferably CMR.

STUDY LIMITATIONS. Because of the observational nature of the study, no causal relations can be assumed between silent MI and long-term prognosis. Although it is conceivable that silent MI increases the risk of cardiovascular complications through increased myocardial damage and LV dysfunction, it might be that the occurrence of silent MI is an indication of more severe comorbidity, poor disease management, or tendency of patients to avoid medical care. Ideally, cardiovascular-specific mortality should be measured in addition to all-cause mortality to provide more insight into possible pathophysiological mechanisms. The major issue with measuring cardiovascular mortality is that the cause of death is often unclear, in addition to the difficulty of defining cardiovascular mortality, whereas determining all-cause death is objective, reliable, and pragmatic.

The association of silent MI and greater risk of MACE was mainly driven by increased mortality. Although AMI and ischemic stroke during follow-up were also more frequent in the silent MI group, these differences were not statistically significant and coronary artery bypass grafting occurred only in patients without silent MI. This might be explained by the low event rate of MACE endpoints other than death. Our sample size may have been insufficient to investigate the relationship of silent MI with each individual MACE endpoint.

Lastly, other possible causes of contrast enhancement in territories other than the current acute infarction may be considered. Distal embolization was differentiated from silent MI by pattern of late contrast enhancement (wedge-shaped spot vs. subendocardial to transmural). Also, nonischemic cause of contrast enhancement was excluded by visual assessment of late contrast enhancement pattern by an experienced reader.

CONCLUSIONS

In patients presenting with seemingly first AMI, 8.2% of patients showed previous silent MI by LGE-CMR. Moreover, the presence of silent MI was a strong, independent predictor of worse long-term prognosis with a more than 3-fold risk of mortality and MACE. These results underline the need for clinicians to recognize these patients as a high-risk subgroup. Future studies are warranted to further investigate pathophysiological mechanisms, preferably using follow-up CMR for LV remodeling and functional impairment over time.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence of previous silent MI in patients presenting with AMI indicates a more than 3-fold risk of mortality and MACE, independent from traditional prognosticators, such as LV ejection fraction and infarct size.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: To optimize secondary prevention after AMI clinicians might consider more strict monitoring or cardioprotective medical therapy in those with silent MI.

TRANSLATIONAL OUTLOOK 1: Consideration of silent MI as possible confounder is warranted in studies investigating prognosis or therapeutic interventions in AMI.

TRANSLATIONAL OUTLOOK 2: Future studies should investigate the development of LV dilatation and functional impairment over time in patients with silent MI with serial cardiac imaging.

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017;39:119–77.

3. Schelbert EB, Cao JJ, Sigurdsson S, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA 2012;308:890–7.

4. Schmid M, Daniel WG, Achenbach S. Cardiovascular magnetic resonance evaluation of the patient with known or suspected coronary artery disease. Heart 2010;96:1586–92.

5. Valensi P, Lorgis L, Cottin Y. Prevalence, incidence, predictive factors and prognosis or silent myocardial infarction: a review of the literature. Arch Cardiovasc Dis 2011;104:178–88.

6. Turkbey EB, Nacif MS, Guo M, et al. Prevalence and correlates of myocardial scar in a US cohort. JAMA 2015;314:1945–54.

7. Kim HW, Klem I, Shah DJ, et al. Unrecognized non-Q-wave myocardial infarction: prevalence and prognostic significance in patients with suspected coronary disease. PLoS Med 2009;6:e1000057.

8. Kehl DW, Farzaneh-Far R, Na B, Whooley MA. Prognostic value of electrocardiographic detection of unrecognized myocardial infarction in persons with stable coronary artery disease: data from the Heart and Soul Study. Clin Res Cardiol 2011;100:359–66.

9. Barbier CE, Themudo R, Bjerner T, Johansson L, Lind L, Ahlstrom H. Long-term prognosis of unrecognized myocardial infarction detected with cardiovascular magnetic resonance in an elderly population. J Cardiovasc Magn Reson 2016;18:43.

10. Toma M, Fu YL, Ezekowitz JA, et al. Does silent myocardial infarction add prognostic value in ST-elevation myocardial infarction patients without a history of prior myocardial infarction? Insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) Trial. Am Heart J 2010;160:671–7.

11. Thygesen K, Alpert JS, White HD. Joint ESC/ACC/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.

12. Nordenskjold AM, Hammar P, Ahlstrom H, et al. Unrecognized myocardial infarction assessed by cardiac magnetic resonance imaging: prognostic implications. PLoS One 2016;11:e0148803.

13. Barbier CE, Bjerner T, Hansen T, et al. Clinically unrecognized myocardial infarction detected at MR imaging may not be associated with atherosclerosis. Radiology 2007;245:103–10.

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