International Journal of Cardiology 261 (2018) 18–23

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease☆

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ARTICLE INFO

Article history:
Received 24 October 2017
Received in revised form 17 January 2018
Accepted 12 March 2018
Available online 14 March 2018

Keywords:
Myocardial infarction
Myocardial infarction with non-obstructive coronary arteries
Predictors

ABSTRACT

Background: Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCAs) is an increasingly recognized entity. No previous study has evaluated predictors for new major adverse cardiacvascular events (MACEs) and death in patients with MINOCA.
Methods: We conducted an observational study of MINOCA patients recorded between July 2003 and June 2013 and followed until December 2013 for outcome events. Out of 199,163 MI admissions, 9092 consecutive unique patients with MINOCA were identified. The mean age was 65.5 years and 62% were women. MACE was defined as all-cause mortality, rehospitalization for acute MI, ischemic stroke and heart failure. Hazard ratio and 95% confidence interval (HR; 95% CI) was calculated using Cox-regression.
Results: A total of 2147 patients (24%) experienced a new MACE and 1254 patients (14%) died during the mean follow-up of 4.5 years. Independent predictors for MACE after adjustment, were older age (1.05; 1.04–1.06), diabetes (1.44; 1.21–1.70), hypertension (1.25; 1.09–1.43), current smoking (1.38; 1.15–1.66), previous myocardial infarction (1.38; 1.04–2.82), previous stroke (1.69; 1.35–2.11), peripheral vascular disease (1.55; 1.97–2.23), chronic obstructive pulmonary disease (1.63; 1.32–2.00), reduced left ventricular ejection fraction (2.00; 1.54–2.60), lower level of total cholesterol (0.88; 0.83–0.94) and higher level of creatinine (1.01; 1.00–1.03). Independent predictors for all cause death were age, current smoking, diabetes, cancer, chronic obstructive pulmonary disease, previous stroke, reduced left ventricular fraction, lower level of total cholesterol and higher levels of creatinine and CRP.
Conclusions: The clinical factors predicting new MACE and death of MINOCA patients seem to be strikingly similar to factors previously shown to predict new cardiovascular events in patients with MI and obstructive coronary artery disease.

1. Introduction

Acute myocardial infarction (MI) is a life threatening condition, which requires immediate management, investigation and treatment. Early fundamental studies have demonstrated a close connection between the atherosclerotic process and the pathogenesis of MI [1,2]. However, large-scale use of acute coronary angiography has revealed that a significant proportion of the patients with MI do not have obstructive coronary artery disease (CAD) as judged by angiography (≥50% diameter stenosis). The term "myocardial infarction with non-obstructive coronary arteries" (MINOCAs) has been coined for this entity [3,4]. A recent position paper from an ESC working group has suggested the following diagnostic criteria for MINOCA [4]; MI criteria met according to the third universal definition of acute MI [5], non-obstructive coronary arteries on angiography (i.e. no coronary artery stenosis ≥ 50%) and no clinically overt specific cause for the acute presentation. Thus, MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes.

MINOCA patients form a heterogenic group, consisting of subgroups with different underlying pathophysiological mechanisms such as plaque rupture, coronary dissection, coronary artery spasm, type 2 MI and clinically unrecognized myocarditis or Takotsubo cardiomyopathy [4,6,7]. Recent meta-analyses have indicated that myocarditis and Takotsubo cardiomyopathy may be common underlying causes of MINOCA, but that correct diagnoses are lacing due to low use of imaging

☆ Acknowledgment of grant support: The SWEDHEART registry is supported by the Swedish Society of Cardiology, the Swedish Society of Thoracic Radiology, the Swedish Society of Thoracic surgery and the Swedish Heart Association. The regestry is financed by the government and the Swedish Association of Local Authorities and Regions (SALAR).
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https://doi.org/10.1016/j.ijcard.2018.03.056

techniques such as cardiac magnetic resonance (CMR) [6,8]. The prevalence of MINOCA is therefore closely dependent on the definition used and ranges between 1 and 14% in different studies [6,7,9–11], with an overall prevalence of 6% in recently published meta-analysis [6]. Although, MINOCA patients seem to have a somewhat better short- and long-term prognosis than patients with MI associated with obstructive CAD (MI-CAD) [6], the prognosis is not benign; we have recently shown that as many as 24% of MINOCA patients experience a MACE within 4 years [11].

Given the heterogeneity of the MINOCA patients, it would be desirable to be able to use clinical predictors to identify patients with different risks for new cardiovascular events and fatal outcome. Therefore, we investigated potential predictors of major adverse cardiovascular events (MACEs) and death in patients with MINOCA.

2. Methods

2.1. Study population

The study population has been previously described [11]. In short, 9092 unique patients with MINOCA were identified among the 199,163 acute MI admissions recorded in the SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in heart disease Evaluated According to Recommended Therapy) between July 1, 2003, and June 30, 2013. Patients were identified as having MINOCA if the discharge diagnosis was acute MI (International Classification of Diseases, 10th Reversion code: I21-I22) and a coronary angiography performed during the index hospitalization that did not show a diameter stenosis of 50% or more.

The cohort consisting of all 9092 MINOCA patients was used for estimating predictors of mortality, a second cohort consisting of the 9003 patients who survived the hospital stay and first 30 days post discharge for estimating the predictors of MACE (Supplemental Fig. 1).

2.2. Outcome definitions

The primary outcome MACE was defined as a composite of all-cause death, rehospitalization for MI, ischemic stroke and heart failure. Additional secondary outcomes were all-cause death and cardiovascular death.

Data on all-cause death (i.e. cardiac, non-cardiac or unknown) was obtained from the Swedish population register, which includes information on the vital status of all Swedish residents. Data on cardiovascular death, defined as International Classification of Diseases-10 codes (ICD) I00-I78, was obtained from the Cause-of-Death Register. Data on myocardial infarction (I21-I23), heart failure (I50, K761, I971, I110), and ischemic stroke (I63, I64) were obtained from the National Patient register, including all ICD codes from all hospital admissions in Sweden.

2.3. Follow-up

Follow-up data became available by merging data from the mandatory Swedish Cause of Death Register and the National Patient Register with the SWEDEHEART registry containing data on baseline characteristics, electrocardiographic (ECG) changes, biochemical markers, coronary angiography results, left ventricular ejection fraction (LVEF), medical and invasive treatment and outcome (see http://www.swedeheart.se for details). The merging was performed at the National Board of Health and Welfare in Sweden based on the personal identification number that all Swedish citizens and all permanent residents of Sweden have. Survival was monitored from admission, and MACE registered from 30 days after discharge until December 31, 2013, with a mean follow-up of 4.5 years. The minimum follow-up was 6 months.

To ensure the quality of the data entered into the SWEDHEART database, a monitor visit is performed at each hospital every second year. Over the years there has been a >95% agreement between data in the registry and in the hospital records [12]. According to Swedish law, all patients must be informed about their participation in the registry. The study was approved by the Regional Ethical Review Board in Stockholm (2012/60-31/2).

2.4. Statistics

Normally distributed continuous variables are presented as mean ± standard deviation (SD). Not normally distributed continuous variables are presented as median and inter quartile range (IQR). The students' *t*-test was used for comparison of normally distributed data and the Mann Whitney *U* test was used for not normally distributed data. The categorical variables are presented as frequency values and comparisons were made using the Chi-square test.

In order to identify the clinical characteristics associated with the primary and secondary outcomes, univariate and multivariate Cox regression analyses were performed. Three different multivariable models were created due to large number of missing data for certain variables and only patients with complete data were included in the analyses. Model 1 included known risk factors for cardiovascular morbidity such as gender, age, diabetes, hypertension, smoking status, previous MI, previous stroke and ECG changes at admission. Model 2 included, in addition to all factors in model 1, the levels of creatinine, CRP and total cholesterol during the index hospitalization. Model 3 included, in addition to all factors in model 2, LVEF measured during index stay and serious non-cardiac diseases (chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), dementia and cancer). Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated using the Cox proportional hazard model. Survival probabilities were calculated using Kaplan-Meier methodology. Stratified analyzes were performed of the association between cholesterol level and outcome in strata according to statin treatment at admission and discharge. Age and cholesterol were also analyzed as categorical variables to identify potential non-linear associations with the outcome. All statistical tests are two-tailed and $p < 0.05$ is regarded as statistically significant. Data analyses are performed using SAS Software Version 9.4 (SAS Institute, Cary, NC, USA) and the Predictive Analytical SoftWare (PASW statistics 17.03) program (SPSS Inc., Chicago, IL, USA).

3. Results

The clinical characteristics of the 9092 patients with MINOCA are shown in Table 1; the mean age was 65.5 ± 11.5 years and 62% were women.

A total of 2147 patients (24.0%) experienced at least one new MACE during a mean follow-up of 4.5 years. The total number of events during follow-up were; 1254 deaths, 624 new MIs, 403 ischemic strokes and 580 hospitalizations with congestive heart failure. Of the 1165 deaths occurring after the first 30 days, only 497 (42.7%) were classified as cardiovascular deaths. During the index hospital stay 68 patients (0.7%) died, the one month mortality rate was 1.0% (89 patients) and the six-month mortality rate was 2.4% (219 patients). Fig. 1 shows, after the first month, a linear mortality risk throughout the follow-up period, while the risk of MACE was higher during the first year and thereafter somewhat lower but constant.

3.1. Clinical predictors of MACE

The following factors were statistically significant univariate predictors of MACE (Supplemental Table 1): older age, diabetes, hypertension, previous smoking, previous MI, previous stroke, COPD, PVD, dementia, previous or present cancer, ECG changes at admission, reduced LVEF, higher levels of creatinine, higher levels of CRP and lower levels of total cholesterol.

The prognostic value of clinical factors, biochemical markers and LVEF was assessed by multivariate Cox regression in three different models (Table 2). In the fully adjusted model (model 3), older age, diabetes, hypertension, current smoking, previous MI, PVD, COPD, previous stroke, low LVEF, higher levels of creatinine and lower levels of total cholesterol remained statistically significantly associated with the outcome.

When age was analyzed as a categorical variable the risk of MACE increased by each age group; <50 years (reference), 50–60 years (HR 1.15 95% CI 0.91–1.44), 60–70 years (HR 2.33 95% CI 1.90–2.85), 70–80 years (HR 4.11 95% CI 3.37–5.01) and > 80 years (HR 6.26 95% CI 5.03–7.80).

The inverse association between total cholesterol levels and MACE was further investigated by dividing the cholesterol levels into three categories (<4 mmol/L, 4–6 mmol/L and >6 mmol/L) and by stratifying according to statin use at admission and statins prescribed at discharge. The association did not remain significant in the 1403 patients without statins at both admission and at discharge or in the 1639 patients with statins at both admission and discharge, while the association remained highly significant for those 5878 patients without statin at admission but with a prescription of statins at discharge (Supplemental Table 2). In multivariate analysis (model 3) the cholesterol level remained associated with MACE only in those with no statin at admission but a prescription of statins at discharge, HR 0.70, 95% CI 0.55–0.88 for total cholesterol 4–6 mmol/L ($p = 0.002$) and HR 0.65, 95% CI 0.49–0.86 for total cholesterol >6 mmol/L ($p = 0.002$).

3.2. Clinical predictors for long-term all-cause-mortality

The following factors were statistically significant univariate predictors of all-cause mortality: older age, diabetes, hypertension, previous

Table 1
Baseline data.

	All MINOCAs	MINOCA Survived > 30 days	MINOCA Died ≤ 30 days	p-Value*
Total, n	**9092**	**9003**	**89**	
Demographics				
Female (%)	62.0	62.1	51.4	0.25
Age, y (±SD)	65.5 ± 11.5	65.4 ± 11.5	72.1 ± 11.6	<**0.001**
Risk factors (%)				
Smoking				
Current	18.8	18.8	20.5	<**0.001**
Previous	30.5	30.5	22.7	
Diabetes	11.6	13.6	15.7	0.53
Hypertension	48.2	48.0	62.9	0.05
Medical history, %				
Cancer	2.0	2.0	4.5	0.09
COPD	8.3	8.4	5.6	0.35
Dementia	0.2	0.2	1.1	0.06
MI	4.6	4.5	9.0	**0.001**
PVD	1.9	1.9	1.1	0.60
Stroke	5.4	5.4	12.4	**0.04**
ECG findings (%)				
ST-elevation	16.4	16.1	50.0	<**0.001**
ST-depression	16.0	16.0	10.2	
T wave abnormalities	13.0	12.9	17.0	
Laboratory findings				
Creatinine, μmol/L (±SD)	80.8 ± 39.3	80.6 ± 39.1	100.1 ± 48.1	<**0.001**
CRP mg/L (IQR)	5.0 (3.0–10.0)	5.0 (3.0–10.0)	10.0 (4.0–44.8)	<**0.001**
LDL cholesterol, mmol/L (±SD)	3.0 ± 1.0	3.0 ± 1.0	2.8 ± 1.7	0.11
Total cholesterol, mmol/L (±SD)	5.1 ± 1.2	5.1 ± 1.2	4.9 ± 1.4	0.15
Examination findings				
LVEF (%)				
≥50%	54.9	55.2	23.6	<**0.001**
40–49%	12.4	12.5	5.6	
30–39%	6.8	6.8	12.4	
<30%	3.2	3.0	18.0	
Unknown	22.6	22.4	40.4	
Medication at admission (%)				
Aspirin	23.4	23.2	35.6	**0.007**
ACE-inhibitors or ARB	27.7	27.6	39.0	**0.03**
Beta-blockers	27.6	27.5	36.8	0.06
Statin	19.0	19.0	18.4	0.89

ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; ECG: electrocardiography, LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PVD: peripheral vascular disease.
* p-Value: difference between MINOCA who died during hospitalization or within 30 days post discharge and MINOCA who survived hospitalization and >30 days post discharge.
Statistical significant differences are written in bold.

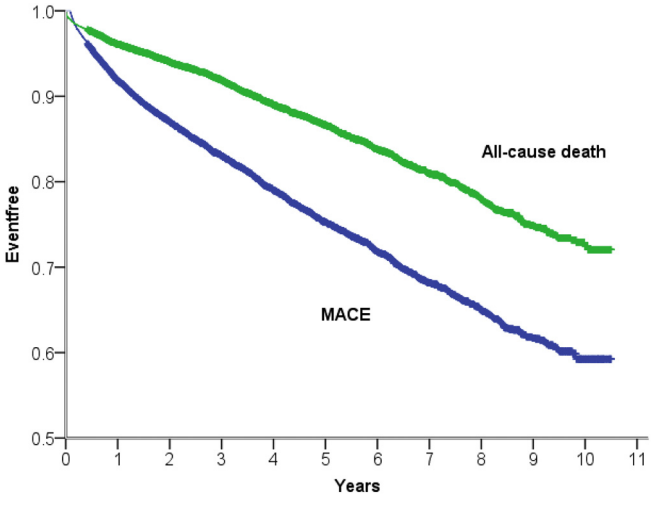

Fig. 1. Cumulative probability for event free survival. The lower blue line demonstrates all-cause death and the upper green line MACE.

smoking, previous MI, previous stroke, previous or present cancer, COPD, PVD, dementia, ECG changes at admission, reduced LVEF, higher levels of creatinine, higher levels of CRP and lower levels of total cholesterol (Supplemental Table 3).

The prognostic value of clinical factors, previous history, biochemical markers and LVEF for the overall mortality was assessed by multivariate Cox regression in three different models (Table 3). In the fully adjusted model, older age, diabetes, current smoking, previous stroke, previous or present cancer, COPD, reduced LVEF, lower levels of total cholesterol, higher levels of creatinine and CRP remained statistically significantly associated with all-cause mortality.

3.3. Predictors for short term mortality

The 89 patients dying in-hospital or within the first 30 days after discharge were older compared to patients who survived the first 30 days post discharge; the prevalence of smoking, previous MI, ECG changes at admission, reduced LVEF and the levels of creatinine and CRP were significantly different between the groups (Table 1). However, the rates of hypertension, diabetes and previous stroke were similar between the two groups. Because of the low number of short-term deaths we refrained from further multi-variable modeling.

Table 2
Multivariate analysis for MACE. Only patients with complete data are included. Model 1 contains 8371 patients, model 2 contains 6102 patients and model 3 contains 4996 patients. Statistical significant differences are written in bold.

	Model 1			Model 2			Model 3		
	HR	CI HR	p-Value	HR	CI HR	p-Value	HR	CI HR	p-Value
Gender, male	1.26	1.15–1.39	<**0.001**	1.14	1.00–1.28	**0.045**	1.13	0.98–1.30	0.101
Age	1.06	1.05–1.06	<**0.001**	1.05	1.05–1.06	<**0.001**	1.05	1.04–1.06	<**0.001**
Smoking									
Previous	1.16	1.04–1.28	**0.005**	1.18	1.04–1.34	**0.011**	1.07	0.92–1.24	0.364
Current	1.53	1.35–1.74	<**0.001**	1.54	1.32–1.80	<**0.001**	1.38	1.15–1.66	**0.001**
Diabetes	1.78	1.41–1.77	<**0.001**	1.45	1.25–1.68	<**0.001**	1.44	1.21–1.70	<**0.001**
Hypertension	1.26	1.14–1.38	<**0.001**	1.27	1.13–1.43	<**0.001**	1.25	1.09–1.43	**0.001**
Cancer							1.37	0.94–1.98	0.104
COPD							1.63	1.32–2.00	<**0.001**
Dementia							2.75	0.87–8.72	0.086
MI	1.93	1.65–1.26	<**0.001**	1.78	1.48–2.29	<**0.001**	1.38	1.04–1.82	**0.025**
PVD							1.55	1.97–2.23	**0.019**
Stroke	1.78	1.53–2.07	<**0.001**	1.67	1.38–2.03	<**0.001**	1.69	1.35–2.11	<**0.001**
ECG changes									
ST elevation	1.18	1.04–1.35	**0.014**	1.04	0.96–1.34	0.136	0.93	0.76–1.13	0.458
ST depression	1.22	1.07–1.40	**0.003**	1.15	0.98–1.36	0.092	1.09	0.90–1.32	0.383
T wave changes	1.26	1.09–1.45	**0.002**	1.20	1.00–1.43	**0.047**	1.09	0.89–1.33	0.427
Other	1.51	1.32–1.72	<**0.001**	1.48	1.26–1.74	<**0.001**	1.33	1.11–1.60	**0.002**
Creatinine				1.02	1.01–1.03	**0.001**	1.01	1.00–1.03	**0.027**
CRP				1.02	1.01–1.04	0.060	1.01	1.00–1.03	0.241
Total cholesterol				0.91	0.86–0.96	<**0.001**	0.88	0.83–0.94	<**0.001**
LVEF									
40–49%							1.31	1.11–1.54	**0.001**
30–39%							1.56	1.29–1.92	<**0.001**
<30%							2.00	1.54–2.60	<**0.001**

3.4. Clinical predictors for new myocardial infarction

Independent predictors for new MI after adjustment were older age (HR 1.01, 95% CI 1.00–1.03), current smoking (HR 1.46, 95% CI 1.06–2.01), hypertension (HR 1.31 95% CI 1.02–1.67), previous MI (HR 2.42 95% CI 1.56–3.75) and higher levels of creatinine (HR 1.02 95% CI 1.01–1.04).

3.5. Clinical predictors for heart failure

Independent predictors for rehospitalization for heart failure after adjustment were older age (HR 1.05, 95% CI 1.03–1.06), diabetes (HR 1.79, 95% CI 1.33–2.41), PVD (HR 1.97 95% CI 1.08–3.59), reduced LVEF during the index hospitalization (LVEF 40–49% HR 2.36 95% CI 1.73–3.20, LVEF 30–39% HR 3.13 95% CI 2.22–4.41, LVEF <30% HR 4.59

Table 3
Multivariate analysis for all-cause mortality. Model 1 consists of 8443 patients, model 2 consists of 6130 patients and model 3 consists of 5013 patients. Statistically significant differences are written in bold.

	Model 1			Model 2			Model 3		
	HR	95 CI	p-Value	HR	95 CI	p-Value	HR	95 CI	p-Value
Male gender	1.39	1.23–1.58	<**0.001**	1.15	0.98–1.36	0.092	1.20	0.98–1.45	0.073
Age	1.08	1.07–1.09	<**0.001**	1.08	1.07–1.09	<**0.001**	1.07	1.06–1.09	<**0.001**
Smoking									
Previous	1.28	1.12–1.47	**0.001**	1.30	1.10–1.55	**0.003**	1.09	0.89–1.34	0.417
Current	1.96	1.66–2.32	<**0.001**	1.85	1.50–2.29	<**0.001**	1.53	1.19–1.99	**0.001**
Diabetes	1.57	1.33–1.84	<**0.001**	1.40	1.13–1.73	**0.002**	1.36	1.05–1.75	**0.018**
Hypertension	1.13	0.99–1.30	0.076	1.15	0.97–1.38	0.109	1.12	0.91–1.37	0.274
Cancer							2.40	1.58–3.61	<**0.001**
COPD							2.33	1.80–3.01	<**0.001**
Dementia							2.37	0.57–9.86	0.236
MI	1.49	1.21–1.83	<**0.001**	1.37	1.03–1.83	**0.032**	1.09	0.75–1.58	0.669
PVD							1.37	0.85–2.19	0.202
Stroke	1.72	1.41–2.09	<**0.001**	1.44	1.11–1.88	**0.007**	1.53	1.13–2.09	**0.007**
ECG changes									
ST elevation	1.43	1.20–1.71	<**0.001**	1.25	1.00–1.58	0.051	0.89	0.68–1.17	0.417
ST depression	1.30	1.09–1.56	**0.004**	1.17	0.93–1.47	0.182	1.13	0.87–1.47	0.368
T wave changes	1.46	1.21–1.76	<**0.001**	1.32	1.04–1.69	**0.023**	1.08	0.82–1.43	0.593
Other	1.57	1.31–1.87	<**0.001**	1.49	1.20–1.87	**0.001**	1.14	0.88–1.48	0.334
Creatinine				1.02	1.00–1.03	**0.009**	1.02	1.00–1.03	**0.030**
CRP				1.04	1.01–1.06	**0.001**	1.03	1.01–1.06	**0.005**
Cholesterol				0.86	0.80–0.93	<**0.001**	0.83	0.77–0.91	<**0.001**
LVEF									
40–49%							1.27	1.02–1.60	**0.037**
30–39%							1.53	1.17–2.00	**0.002**
<30%							2.16	1.55–3.01	<**0.001**

COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PVD: peripheral vascular disease; ECG: electrocardiography; LVEF: left-ventricular ejection fraction.

95% CI 3.05–6.91), higher levels of creatinine (HR 1.02 95% CI 1.00–1.03) and lower levels of cholesterol (HR 0.87 95% CI 0.78–0.97).

3.6. Clinical predictors for ischemic stroke

Independent predictors for rehospitalization for ischemic stroke after adjustment were older age (HR 1.06, 95% CI 1.05–1.08), diabetes (HR 1.47, 95% CI 1.02–2.13), previous stroke (HR 4.27 95% CI 2.93–6.22) and lower levels of cholesterol (HR 0.85 95% CI 0.74–0.97).

4. Discussion

The present study is, to the best of our knowledge, the first one to identify independent clinical risk factors for MACE as well as for mortality in a large cohort of patients with MINOCA. Among 9092 consecutive MINOCA patients followed for a mean of 4.5 years we can report that older age, current smoking, diabetes, hypertension, COPD, previous MI, previous stroke, previous PVD, low LVEF, high levels of creatinine and lower levels of total cholesterol were independently associated with MACE. The clinical factors associated with long-term mortality were similar to those for MACE except that presence of previous or present cancer and high levels of CRP also influenced mortality while hypertension, previous MI and previous PVD did not.

4.1. Clinical characteristics of the present MINOCA cohort

The mean age in the present study was 65.5 years which is higher than that in previous smaller studies where the mean age has ranged between 52.0 and 60.3 years [6,8,13]; 62% were women in line with some other MINOCA studies [8,13], but in contrast to the systemic review which reported a distribution of 60% men and 40% women [6]. The difference in gender distribution may partly be explained by different age distributions [6]. The prevalence of co-morbidities like hypertension, hyperlipidemia and diabetes were high like in other MINOCA studies [6,13,14]. In the present study 16.4% of the patients presented with a STEMI, which is in accordance with the SMINC study in which 18.0% presented with STEMI [14], but considerably lower than the 30% with STEMI in the general MI population in Sweden [15] and the 33% with STEMI in the meta-analysis of MINOCA studies [6]. The prevalence of ST-elevation was significantly higher in patients who died during hospitalization or <30 days from discharge compared to patients who survived >30 days post discharge (50.0% vs. 16.1%).

4.2. MINOCA and clinical predictors for adverse outcome

Clinical characteristics such as older age, diabetes, hypertension and smoking were associated with new MACE in patients with MINOCA. Our findings are strikingly consistent with findings from large epidemiological studies conducted half a century ago as well as a more recent case-control study identifying factors associated with CAD [16–18]. The associations between an increased level of CRP as well as an increased level of creatinine and a new MACE are also consistent with previous findings in studies of patients with CAD [19–21]. Most independent risk factors proved to be similar for both MACE and all-cause death with the exception of dementia which was only associated with all-cause death.

We report a long-term mortality for the MINOCA patients in the present study of 14.0% (mean follow-up period 4.5 years) and an in-hospital mortality of 0.7%, which are in line with the previous meta-analysis of MINOCA patients reporting an in-hospital mortality of 0.9% and a one-year mortality rate of 4.7% [6]. The MINOCA patients in the present study, as well as in previous studies [6] seem to have a better short- and long-term prognosis than patients with MI-CAD. However, the long term prognosis for MINOCA patients is considerably worse than the annual mortality of 0.3% for patients with stable chest pain in the absence of obstructive CAD [22] and in some studies equivalent to those with an MI associated with single or double- vessel CAD [23]. The rate of long-term serious cardiovascular events are therefore of concern, considering that MINOCA patients tend to be younger and have less comorbidities than patients with MI-CAD [6,11]. The comparisons of prognosis between patients with MINOCA and patients with MI-CAD is challenging owing to the differences in the underlying pathophysiological mechanisms. MINOCA patients form a heterogenic population with many different possible underlying mechanisms in contrast to MI-CAD for which the thrombo-atherosclerotic mechanism dominates. However, when controlled for age, there were no clear sex-related differences in long-term mortality for patients with MINOCA similarly to findings in MI-CAD patients from the SWEDEHEART registry [24]. Also a higher short-term mortality in patients presenting as STEMI compared to NSTEMI, which is well-known in MI-CAD patients, was seen in the MINOCA patients in the present study.

Our data on all-cause mortality among the limited number of patients with dementia and cancer must also be interpreted with caution since these conditions are associated with increased disease specific mortality.

4.3. The cholesterol paradox

In the present study the mean level of total cholesterol (5.1 ± 1.2 mmol/L) was close to the mean level (5.5 ± 1.1 mmol/L) shown in a contemporary Swedish healthy control population; also the percentage of patients on statin treatment was similar (19 vs. 17%) [25]. In previous studies of MINOCA the prevalence of treated dyslipidemia on admission has ranged between 21 and 33% [6,13,14].

We were able to demonstrate that even after adjustment, low levels of total cholesterol were significantly associated with the composite endpoint of MACE as well as with long-term mortality. This finding might seem to be in conflict with previous large studies demonstrating hypercholesterolemia as a causal factor for CAD and that lowering of total cholesterol and LDL reduces cardiovascular risk in both the primary and secondary prevention settings [16–18,26–28]. However, our finding of a cholesterol paradox is in accordance with findings in the elderly [29], patients with ischemic stroke [30], rheumatoid arthritis [31] as well as patients with acute MI [32,33].

When the association between cholesterol level and MACE in the present cohort was stratified according to the use of statins, only the cholesterol level in patients without statins at admission but with a prescription of statins at discharge continued to be independently associated with MACE. Thus, the phenomenon is primarily seen in the statin naïve who receive statin treatment after MINOCA. Differences in underlying pathophysiological mechanisms between MINOCA patients with initial low- and high- cholesterol levels may be a possible explanation for this finding. The development of MINOCA in patients with low initial cholesterol levels (<4 mmol/L) may to a lesser degree be associated with the cholesterol level, and hence, initiating statin treatment in these patients might have minor effects on the risk for new events. On the other hand, in patients with higher cholesterol levels (≥4 mmol/L), initiating statin treatment might decrease the risk of new events substantially, giving rise to the paradoxical finding that higher initial cholesterol levels are associated with a favorable prognosis. This explanation might also fit with our previous results showing that statin treatment is beneficial and decreases the risk of MACE in the general MINOCA population [10]. However, there might also be other or additional, so far unknown, explanations for this paradox.

5. Limitations

Our study has some limitations that need to be considered. The data available in SWEDEHEART do not permit separation of patients into those without angiographic signs of coronary lesions and those with signs of coronary lesions but no stenosis of ≥50%. Studies have indicated

that these subgroups constitute around 50% each of the MINOCA population [12]. Coronary angiographies were evaluated locally at each hospital and not at a core laboratory. We lack sufficient information on the results of examinations such as FFR data on the fractional flow reserve, optical coherence tomography, left ventricular angiography and CMR to be able to divide the present MINOCA cohort into groups depending on possible underlying pathophysiological mechanism. The predictors may be different according to the underlying mechanism. We lack information on the results of examinations performed after the hospitalization period. Some MINOCA patients in our cohort may thus, have subsequently been diagnosed with myocarditis on the basis of CMR performed after hospital discharge. There might also be some cases of Takotsubo cardiomyopathy in the cohort, especially during the first years of the study period where the awareness of this condition was limited. The medical therapy at discharge was at the discretion of the physician in charge and we lack information on any tailored treatments regarding underlying mechanisms. We lack information about previous or present depressions and other psychiatric disorders.

We were able to provide information on all-cause mortality and on cardiovascular mortality but we had no information on other specific types of mortality contributing to all-cause mortality.

6. Conclusion

The clinical factors predicting new MACE and death of MINOCA patients seem to be strikingly similar to factors previously shown to predict new cardiovascular events in patients with MI and obstructive coronary artery disease.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.03.056.

Acknowledgements

Nermin Hadziosmanovic for compilation of the database and general statistical advice.

Fundings

The Swedish Foundation for Strategic Research.

Conflict of interest

None of the authors reported conflicts of interest relevant to this study.

References

[1] M.A. DeWood, J. Spores, R. Notske, L.T. Mouser, R. Burroughs, M.S. Golden, et al., Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction, N. Engl. J. Med. 303 (16) (1980) 897–902.
[2] M.A. DeWood, W.F. Stifter, C.S. Simpson, J. Spores, G.S. Eugster, T.P. Judge, et al., Coronary arteriographic findings soon after non-Q-wave myocardial infarction, N. Engl. J. Med. 315 (7) (1986) 417–423.
[3] J.F. Beltrame, Assessing patients with myocardial infarction and nonobstructed coronary arteries (MINOCA), J. Intern. Med. 273 (2) (2013) 182–185.
[4] S. Agewall, J.F. Beltrame, H.R. Reynolds, A. Niessner, G. Rosano, A.L. Caforio, et al., ESC working group position paper on myocardial infarction with non-obstructive coronary arteries, Eur. Heart J. 38 (3) (2017) 143–153.
[5] K. Thygesen, J.S. Alpert, A.S. Jaffe, M.L. Simoons, B.R. Chaitman, H.D. White, et al., Third universal definition of myocardial infarction, J. Am. Coll. Cardiol. 60 (16) (2012) 1581–1598.
[6] S. Pasupathy, T. Air, R.P. Dreyer, R. Tavella, J.F. Beltrame, Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries, Circulation 131 (10) (2015) 861–870.
[7] G. Niccoli, G. Scalone, F. Crea, Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management, Eur. Heart J. 36 (8) (2015) 475–481.
[8] P. Tornvall, E. Gerbaud, A. Behaghel, R. Chopard, O. Collste, E. Laraudogoitia, et al., Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data, Atherosclerosis 241 (1) (2015) 87–91.
[9] I. Kardasz, R. De Caterina, Myocardial infarction with normal coronary arteries: a conundrum with multiple aetiologies and variable prognosis: an update, J. Intern. Med. 261 (4) (2007) 330–348.
[10] O. Collste, P. Sorensson, M. Frick, S. Agewall, M. Daniel, L. Henareh, et al., Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study, J. Intern. Med. 273 (2) (2013) 189–196.
[11] B. Lindahl, T. Baron, D. Erlinge, N. Hadziosmanovic, A. Nordenskjold, A. Gard, et al., Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease, Circulation 135 (16) (2017) 1481–1489.
[12] T. Jernberg, M.F. Attebring, K. Hambraeus, T. Ivert, S. James, A. Jeppsson, et al., The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART), Heart 96 (20) (2010) 1617–1621.
[13] H. von Korn, V. Graefe, M.A. Ohlow, J. Yu, B. Huegl, A. Wagner, et al., Acute coronary syndrome without significant stenosis on angiography: characteristics and prognosis, Tex. Heart Inst. J. 35 (4) (2008) 406–412.
[14] M. Daniel, C. Ekenback, S. Agewall, E.B. Brolin, K. Caidahl, K. Cederlund, et al., Risk factors and markers for acute myocardial infarction with angiographically normal coronary arteries, Am. J. Cardiol. 116 (6) (2015) 838–844.
[15] Annual report SWEDEHEART, Scand. Cardiovasc. J. 48 (Suppl. 63) (2012) 2–133.
[16] W.B. Kannel, W.P. Castelli, T. Gordon, P.M. McNamara, Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study, Ann. Intern. Med. 74 (1) (1971) 1–12.
[17] Coronary heart disease in seven countries. Summary, Circulation 41 (Suppl. 4) (1970) I186–95.
[18] S. Yusuf, S. Hawken, S. Ounpuu, T. Dans, A. Avezum, F. Lanas, et al., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, Lancet 364 (9438) (2004) 937–952.
[19] H.C. Pan, W.H. Sheu, W.J. Lee, W.L. Lee, Y.C. Liao, K.Y. Wang, et al., Coronary severity score and C-reactive protein predict major adverse cardiovascular events in patients with stable coronary artery disease (from the Taichung CAD study), Clin. Chim. Acta 445 (2015) 93–100.
[20] S. Sederholm Lawesson, J. Alfredsson, K. Szummer, M. Fredrikson, E. Swahn, Prevalence and prognostic impact of chronic kidney disease in STEMI from a gender perspective: data from the SWEDEHEART register, a large Swedish prospective cohort, BMJ Open 5 (6) (2015), e008188. .
[21] M.P. Winter, H. Blessberger, A. Alimohammadi, N. Pavo, K. Huber, J. Wojta, et al., Long-term outcome and risk assessment in premature acute myocardial infarction: a 10-year follow-up study, Int. J. Cardiol. 240 (2017) 37–42.
[22] D.P. Di Fiore, J.F. Beltrame, Chest pain in patients with 'normal angiography': could it be cardiac? Int. J. Evid. Based Healthc. 11 (1) (2013) 56–68.
[23] W.Y. Kang, M.H. Jeong, Y.K. Ahn, J.H. Kim, S.C. Chae, Y.J. Kim, et al., Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? Int. J. Cardiol. 146 (2) (2011) 207–212.
[24] J. Alfredsson, J. Lindback, L. Wallentin, E. Swahn, Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART), Eur. Heart J. 32 (24) (2011) 3128–3136.
[25] L. Ryden, K. Buhlin, E. Ekstrand, U. de Faire, A. Gustafsson, J. Holmer, et al., Periodontitis increases the risk of a first myocardial infarction: a report from the PAROKRANK Study, Circulation 133 (6) (2016) 576–583.
[26] Cholesterol Treatment Trialists C, C. Baigent, L. Blackwell, J. Emberson, L.E. Holland, C. Reith, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, Lancet 376 (9753) (2010) 1670–1681.
[27] S.Y. Lee, S.J. Oh, E.J. Kim, C.Y. Oum, S.H. Park, J. Oh, et al., Statin intensity and clinical outcome in patients with stable coronary artery disease and very low LDL-cholesterol, PLoS One 11 (11) (2016), e0166246. .
[28] M.J. van den Berg, Y. van der Graaf, G.J. de Borst, L.J. Kappelle, H.M. Nathoe, F.L.J. Visseren, et al., Low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B and cardiovascular risk in patients with manifest arterial disease, Am. J. Cardiol. 118 (6) (2016) 804–810.
[29] I.J. Schatz, K. Masaki, K. Yano, R. Chen, B.L. Rodriguez, J.D. Curb, Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study, Lancet 358 (9279) (2001) 351–355.
[30] I. Markaki, U. Nilsson, K. Kostulas, C. Sjostrand, High cholesterol levels are associated with improved long-term survival after acute ischemic stroke, J. Stroke Cerebrovasc. Dis. 23 (1) (2014) e47–53.
[31] E. Myasoedova, C.S. Crowson, H.M. Kremers, V.L. Roger, P.D. Fitz-Gibbon, T.M. Therneau, et al., Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease, Ann. Rheum. Dis. 70 (3) (2011) 482–487.
[32] K.H. Cheng, C.S. Chu, T.H. Lin, K.T. Lee, S.H. Sheu, W.T. Lai, Lipid paradox in acute myocardial infarction-the association with 30-day in-hospital mortality, Crit. Care Med. 43 (6) (2015) 1255–1264.
[33] V.S. Reddy, Q.T. Bui, J.R. Jacobs, S.M. Begelman, D.P. Miller, W.J. French, et al., Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox), Am. J. Cardiol. 115 (5) (2015) 557–562.