ESC European Society of Cardiology

European Heart Journal (2018) **39**, 91–98
doi:10.1093/eurheartj/ehx667

Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests

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Received 16 May 2017; revised 21 August 2017; editorial decision 27 October 2017; accepted 20 November 2017; online publish-ahead-of-print 8 December 2017

See page 99 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx737)

Aims Functional alterations of epicardial coronary arteries or coronary microcirculation represent a frequent cause of myocardial infarction and non-obstructive coronary arteries (MINOCA). We aimed at assessing the prognostic value of intracoronary provocative tests in patients presenting with MINOCA and in which other causes of MINOCA have been excluded.

Methods and results We prospectively evaluated patients with a diagnosis of MINOCA, excluding patients with aetiologies other than suspected coronary vasomotor abnormalities. Immediately after coronary angiography, an invasive provocative test using acetylcholine or ergonovine was performed. The incidence of death from any cause, cardiac death, and recurrence of acute coronary syndrome (ACS) was assessed at follow-up. We also assessed angina status using Seattle Angina Questionnaires (SAQ). We enrolled 80 consecutive patients [mean age 63.0 ± 10.7 years, 40 (50%) male]. Provocative test was positive in 37 (46.2%) patients without any complication. Among patients with a positive test, epicardial spasm was detected in 24 (64.9%) patients and microvascular spasm in 13 (35.1%) patients. After a median follow-up of 36.0 (range 12.0–60.0) months, patients with a positive test had a significantly higher occurrence of death from any cause [12 (32.4%) vs. 2 (4.7%); $P = 0.002$], cardiac death [7 (18.9%) vs. 0 (0.0%); $P = 0.005$], and readmission for ACS [10 (27.0%) vs. 3 (7.0%); $P = 0.015$] as well as a worse angina status as assessed by SAQ [Seattle score: 88.0 (33.0–100.0) vs. 100.0 (44.0–100.0); $P = 0.001$] when compared with patients with a negative test.

Conclusions We demonstrate that in patients presenting with MINOCA and suspected coronary vasomotor abnormalities, a positive provocative test for spasm is safe and identifies a high-risk subset of patients.

Keywords MINOCA • Invasive provocative test • Vasospasm • Prognosis

Introduction

Myocardial infarction (MI) and non-obstructive coronary arteries (MINOCA) is a syndrome with different causes, characterized by clinical evidence of MI with normal or near-normal coronary arteries on angiography.[1,2] Data from large MI registries suggest a prevalence between 5% and 25%,[2–4] but the most recent study, in a contemporary cohort of patients, reported a prevalence of 8.8%,[5] which appears to reflect daily clinical experience. Of importance, the prognosis of MINOCA is not as benign as reported by early cohort studies and as commonly assumed by physicians.[4,6,7] Moreover, a recent retrospective analysis of patients enrolled in the ACUITY trial[5] showed that, compared with non-ST elevation MI patients and obstructive coronary arteries, patients with MINOCA had a higher

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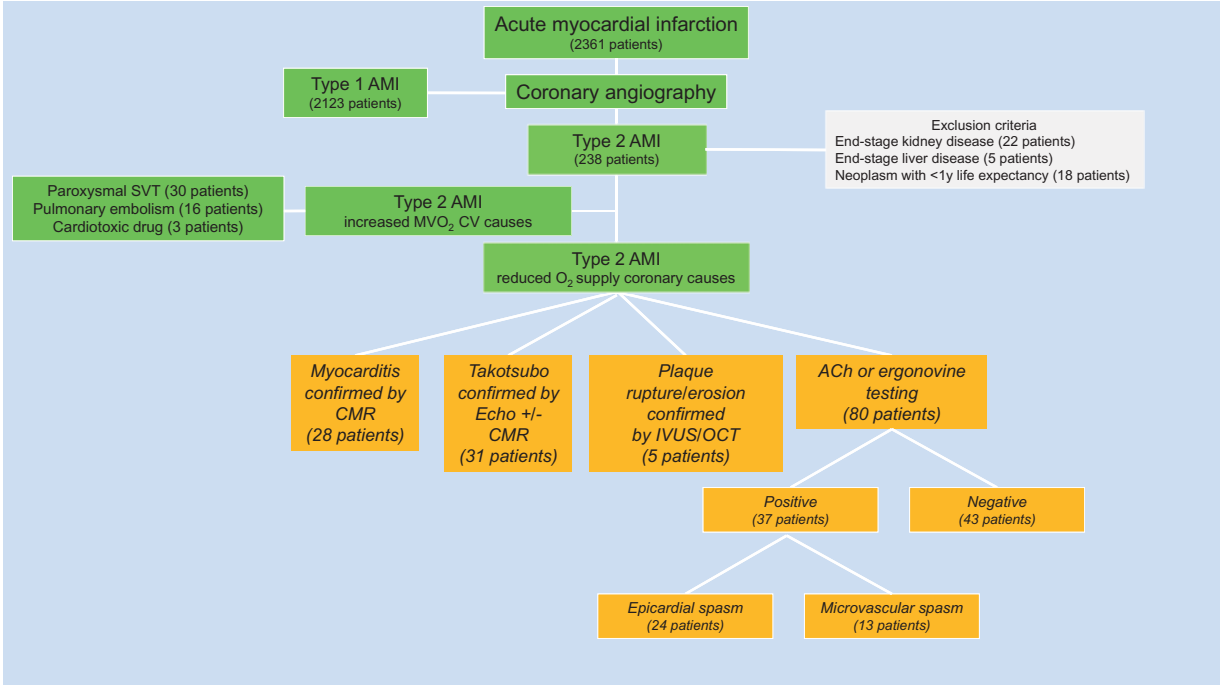

Figure 1 Study flow chart of enrolled patients. FFR assessment was performed in 12 patients presenting with AMI [11 patients had a positive FFR (≤0.80) and were not classified as MINOCA; 1 patient had a negative FFR (>0.80) and was enrolled].AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; CV, cardiovascular; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; SVT, supraventricular tachycardia.

adjusted risk of mortality at 1 year, driven by a greater non-cardiac mortality.

Causes of MINOCA are multiple, such as takotsubo syndrome, myocarditis, paroxysmal supraventricular tachycardia, coronary thrombosis with an underlying mild coronary stenosis or dissection, and coronary embolism.[1] Of importance, functional alterations at the level of epicardial coronary arteries or coronary microcirculation represent a frequent, but often unrecognized, cause of MINOCA.[1,8–10] The prevalence of coronary artery spasm ranges between 3% and 95% of MINOCA patients; this wide difference depends on multiple factors, including the definition of spasm, the ethnic origin of patients, and the stimuli used to unreveal spasm.[11] Coronary microvascular spasm is characterized by transient myocardial ischaemia, as indicated by ST-segment changes and angina, in the presence of non-obstructive coronary arteries. It may be considered the unstable counterpart of chronic microvascular angina.[12] Previous studies showed that about 25% of patients with MINOCA have evidence of microvascular spasm.[13]

Previous studies have also suggested that some subsets of patients with epicardial vasomotor abnormalities have an increased risk of future cardiovascular events,[8,14] whereas angina patients with microvascular spasm seem to have a better outcome.[15] However, while data on the outcome of patients with functional coronary alterations in stable angina patients are abundant, no systematic study has hitherto been carried out in patients with MINOCA.[16,17] This is probably because it is commonly believed that provocative coronary testing in patients with acute MI is potentially dangerous. Accordingly, current guidelines do not recommend these investigations in patients with acute MI.[18–20] In our study, we aimed at assessing the prognostic value of intracoronary provocative tests in patients presenting with MINOCA in whom other specific causes had been excluded.

Methods

Study population

We prospectively evaluated 238 patients undergoing coronary angiography at the Policlinico Agostino Gemelli (Rome, Italy) and having a diagnosis of MI without obstructive coronary artery disease (CAD) (stenosis <50% at coronary angiography). Specifically, patients were initially diagnosed as having MI based on their reporting of one or more episodes of chest pain at rest, typical enough to suggest a cardiac ischaemic origin, in the previous 24 h, associated with ST-segment and/or T-wave abnormalities on the electrocardiogram (ECG) and detection of raise and fall of serum troponin T levels with at least one value exceeding the 99th percentile of a normal reference population with an upper limit of 0.014 μg/L.[21] Exclusion criteria were age <18 years and/or pregnancy (0 patients), end-stage liver diseases (5 patients), renal failure >Stage III according to KDIGO classification (22 patients), and neoplasms with a life expectancy <1 year (18 patients). We also excluded patients with causes of MINOCA other than suspected coronary vasomotor abnormalities and in which provocative test was not performed (*Figure 1*). In particular, we excluded 31 patients with a diagnosis of takotsubo syndrome confirmed by left ventricle angiography, 28 patients with a suspected diagnosis of myocarditis (diagnosis based on the presence of signs and symptoms of infection and/or inflammatory activation associated with wall motion

abnormalities at left ventricular angiography and echocardiogram suggesting a non-epicardial pattern and confirmed by a subsequent cardiac magnetic resonance imaging), 30 patients with paroxysmal atrial fibrillation-related MI, 16 patients with pulmonary embolism, 5 patients without obstructive CAD but with evidence of coronary thrombosis on an unstable plaque confirmed by optical coherence tomography, and 3 patients who underwent cardiotoxic drug administration. Eventually, we included 80 patients. Enrolment period was from January 2010 to June 2016. The study protocol complied with the Declaration of Helsinki, and the study was approved by the institutional review committee. All patients gave written informed consent before angiography.

Procedural details

All patients received aspirin (250 mg intravenously) plus clopidogrel (600 mg orally) or ticagrelor (180 mg orally) or prasugrel (60 mg orally) in the emergency department, whereas heparin (5000 IU) was administered both in the emergency department and, if needed, before coronary angiography according to activated clotting time levels. Coronary angiography was performed within 48 h of admission through femoral or radial access. Absence of CAD was defined as the presence of totally normal coronary arteries. Non-obstructive CAD was defined as the presence of coronary stenosis >0% but <50% of lumen diameter in one or more major epicardial coronary arteries.

Invasive provocative test protocol

The provocative test to assess coronary vasoreactivity was performed immediately after coronary angiography. Acetylcholine (ACh) was administered in a stepwise manner into the left coronary artery (LCA) (20–200 μg) or into the right coronary artery (RCA) (20–50 μg) over a period of 3 min with an interval of 2–3 min between injections. When ergonovine was used, it was administrated as a bolus in a stepwise manner into the LCA (8–64 μg) and RCA (8–40 μg) with an interval of 2–3 min between each injection (doses of vasoactive drugs administered are reported in see Supplementary material online, *Table S1*). Coronary angiography was performed 1 min after each injection of these agents and when chest pain and/or ischaemic ECG changes were observed. Both the decision of selecting the provocative agent and whether the LCA or RCA was challenged as first were left to the discretion of the physicians; both LCA and RCA were tested if the first test was negative. In patients taking vasoactive drugs, the provocation tests were performed after a washout period of at least 24 h for calcium channel blockers (CCBs) and nitrates. The procedure was performed through radial or femoral artery route. In case of radial access, long introducer sheaths were used to avoid the occurrence of spasm, and indeed, no case of radial artery spasm requiring the administration of vasodilator drugs was recorded. Finally, in patients with coronary stenoses between 30% and 50%, assessment of fractional flow reserve (FFR), preceded by intracoronary nitroglycerine administration, was performed after the provocative vasoreactivity test. Patients were diagnosed as MINOCA only if FFR was normal (>0.80), whereas patients were excluded in case of abnormal FFR (≤0.80), indicating the presence of obstructive CAD.

Angiographic responses during the provocative test were assessed in multiple orthogonal views to detect the most severe narrowing and analysed using computerized quantitative coronary angiography (QCA-CMS, version 6.0, Medis-Software, Leiden, The Netherlands). The test was considered positive for epicardial coronary spasm in the presence of focal or diffuse epicardial coronary diameter reduction ≥90% in comparison with the relaxed state following intracoronary nitroglycerine administration given to relieve the spasm, associated with the reproduction of the patient's symptoms and ischaemic ECG shifts. The test was considered negative for epicardial spasm if one of these three components was absent. Microvascular spasm was diagnosed when typical ischaemic ST-segment changes and angina developed in the absence of epicardial coronary constriction ≥90% diameter reduction.[15,22] Occurrence of both brady arrhythmias (defined as bradycardia with heart rate <50 b.p.m. or second- or third-degree atrioventricular block lasting more than 3 s) and ventricular tachycardia (defined as three or more consecutive premature ventricular complexes) during the provocative test was also recorded.

Clinical follow-up

All patients were discharged from the hospital after the index admission with an optimal medical treatment including CCB up-titrated at the highest tolerated doses. Periodical titration of CCB dose with assessment of symptoms and heart rate was planned. The incidence of death from any cause, cardiac death, recurrence of acute coronary syndrome (ACS), and recurrence of angina was assessed at 6, 12, 24, 36, 48 and 60 months by telephonic interview and/or clinical check. We also collected Seattle Angina Questionnaires (SAQ) at 1 year.[23] Cardiac death included sudden death or death preceded by typical chest pain; recurrence of ACS was defined as typical chest pain at rest associated with ST-segment and/or T-wave abnormalities on the ECG and/or detection of increased serum troponin T levels.

Statistical analysis

Data distribution was assessed according to the Kolgormonov–Smirnov test. Continuous variables were compared using an unpaired Student's *t*-test or the Mann–Whitney *U* test, as appropriate, and data were expressed as mean ± standard deviation or as median (range). Categorical data were evaluated using the χ^2 test or the Fisher's exact test as appropriate. All tests were two sided, and a *P*-value of <0.05 represented statistically significant differences.

Survival curves of death from any cause, cardiac death, and readmission for ACS for patients with positive or negative provocative test were produced using the Kaplan–Meier method and were compared by log-rank test. Univariable Cox regression analysis was applied to assess the relation of individual variables with death from any cause. Cox regression was then applied to identify variables independently associated with all-cause mortality; to this aim, we included in the multivariable model only variables showing $P \leq 0.05$ at univariable analysis. All analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and STATA version 11.2 (StataCorp, College Station, TX, USA).

Results

Baseline clinical and angiographic characteristics according to provocative test response

We enrolled 80 patients [mean age 63.0 ± 10.7 years, 40 (50%) male] presenting with MINOCA and undergoing invasive provocative test. Acetylcholine test was performed in 43 (53.7%) patients and ergonovine test in 37 (46.3%) patients. Non-obstructive CAD was detected in 43 (53.7%) patients, whereas angiographically normal coronary arteries were present in 37 (46.3%) patients.

The provocative test was positive in 37 (46.2%) patients, following injection into LCA in 26 patients or into the RCA in 11 patients. During ergonovine or Ach test, transient brady arrhythmias developed in 2.7% ($n = 1$) and 2.3% ($n = 1$) of patients, respectively, and occurred during vasospasm induced in the RCA (brady arrhythmias occurred in 2 of 11 patients with a positive test in the RCA). No ventricular tachycardia occurred. Overall, the rate of

Table 1 Clinical and angiographic characteristics of overall population and according to invasive test response

Characteristics	Total population ($n = 80$)	Positive functional test ($n = 37$)	Negative functional test ($n = 43$)	*P*-value
Clinical characteristics				
Age (years), mean ± SD	63.0 ± 10.7	64.1 ± 12.3	62.0 ± 11.2	0.54
Male gender, *n* (%)	40 (50.0)	17 (45.9)	23 (53.5)	0.50
BMI (kg/m^2), median (range)	24.3 (20.6–26.2)	22.2 (19.1–25.3)	23.5 (20.5–25.4)	0.33
Hypertension, *n* (%)	32 (40)	13 (35.1)	19 (44.2)	0.41
Smoke, *n* (%)	17 (21.3)	6 (16.2)	11 (25.6)	0.31
Hypercholesterolaemia, *n* (%)	19 (23.8)	8 (21.6)	11 (25.6)	0.68
Diabetes, *n* (%)	8 (10.0)	4 (10.8)	4 (9.3)	1.0
Familiar history of cardiovascular diseases, *n* (%)	16 (20.0)	6 (16.2)	10 (23.3)	0.43
Admission therapy, *n* (%)				
Aspirin	20 (25.0)	10 (27.0)	10 (23.3)	0.70
Thienopyridines	9 (11.3)	4 (10.8)	5 (11.6)	1.0
Statins	4 (5.0)	1 (2.7)	3 (7)	0.62
Beta-blockers	9 (11.3)	5 (13.5)	4 (9.3)	0.73
ACE-I and/or ARB,	7 (8.8)	2 (5.4)	5 (11.6)	0.44
CCB	0 (0.0)	0 (0.0)	0 (0.0)	1.0
Nitrates	0 (0.0)	0 (0.0)	0 (0.0)	1.0
Discharge therapy, *n* (%)				
Aspirin	66 (82.5)	31 (83.8)	35 (81.4)	0.78
Thienopyridines	17 (21.2)	6 (16.2)	11 (25.6)	0.31
Statins	42 (52.5)	22 (59.5)	20 (46.5)	0.25
Beta-blockers	28 (35.0)	10 (27.0)	18 (41.9)	0.17
ACE-I and/or ARB	21 (26.2)	10 (27.0)	11 (25.6)	0.88
CCB	44 (55.0)	37 (100.0)	7 (16.3)	<0.001
Nitrates	5 (6.2)	5 (13.5)	0 (0.0)	0.018
HS-TnT peak (μg/L), median (range)	0.090 (0.021; 0.562)	0.100 (0.027; 0.562)	0.080 (0.021; 0.384)	0.049
Non-obstructive coronary atherosclerosis, *n* (%)	43 (53.8)	31 (83.8)	12 (27.9)	<0.001
LVEF (%), median (range)	58 (56–62)	58 (54–62)	58 (56–61)	0.59

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; BMI, body mass index; CCB, calcium channel blockers; HS-TnT, high-sensitivity troponin T; LVEF, left ventricle ejection fraction; SD, standard deviation.

arrhythmic complications among patients with a positive test was 5.4% ($n = 2$), which was comparable to those during spontaneous angina attacks,[24] confirming the safety of performing provocative tests in patients with suspected vasomotion abnormalities also in the context of acute MI. There were no significant differences in baseline clinical characteristics according to the response to the invasive provocative test (*Table 1*). Of note, patients with a positive test presented more frequently a non-obstructive CAD compared with patients with negative test [31 (83.8%) vs. 12 (27.9%); $P < 0.001$]. Moreover, patients with a positive test had a higher peak of high-sensitivity troponin T levels during the index admission [0.100 (0.027–0.562) vs. 0.08 (0.021–0.384) μg/L; $P = 0.049$] (*Table 1*).

Clinical outcome according to provocative test response

All patients with evidence of vasospasm were discharged with the highest tolerated dose of CCB. Of interest, a CCB dose reduction or discontinuation during follow-up occurred in 19 patients (15 of whom had a positive provocative test response) mainly due to symptomatic brady arrhythmias (18 patients) or gastrointestinal intolerance (1 patient). However, there were no significant clinical events related to CCB administration at follow-up (e.g. syncope or readmission for heart failure).

Patients with a positive test had a worse clinical outcome compared with patients with a negative test at a long-term follow-up [median follow-up time 36 (range 12–60) months]. In particular, patients with a positive test had a significantly higher occurrence of both death from any causes [12 (32.4%) vs. 2 (4.7%); $P = 0.002$] and cardiac death [7 (18.9%) vs. 0 (0.0%); $P = 0.005$] compared to patients with a negative test (*Figure 2*). Moreover, patients with a positive test had a higher rate of readmission for ACS [10 (27.0%) vs. 3 (7.0%); $P = 0.015$] and a worse angina status at 1 year as assessed by SAQ [Seattle score: 88.0 (33.0–100.0) vs. 100.0 (44.0–100.0); $P = 0.001$] compared to patients with a negative test (*Table 2*). Incidence rates for death from any causes, cardiac death, and recurrence of ACS are shown in Supplementary material online, *Table S2*. Of importance, among patients with a positive test response, a CCB dose reduction or discontinuation at follow-up occurred in 8 of 12 (66.6%) patients

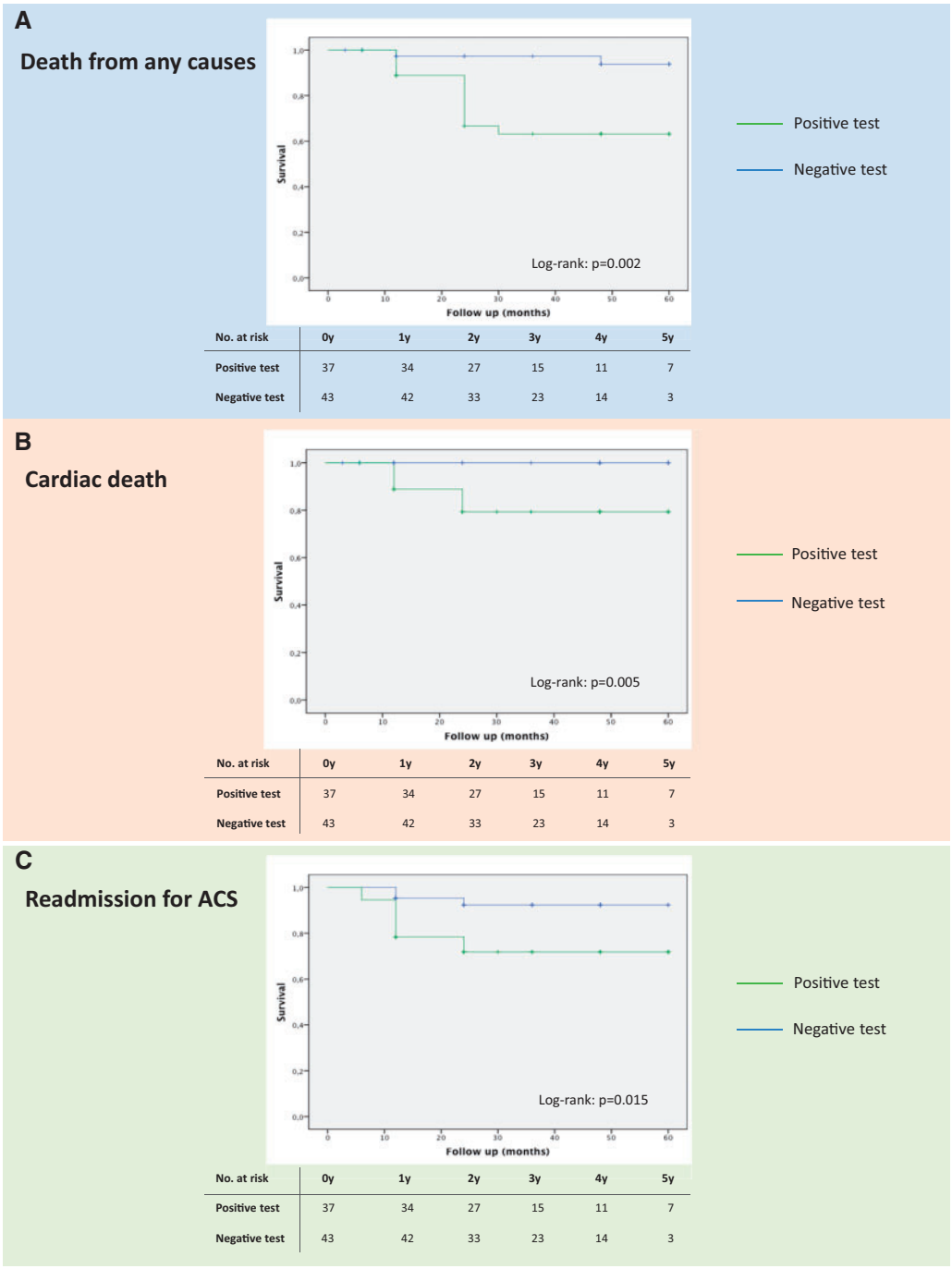

Figure 2 Survival Kaplan–Meier curves for death from any cause (*A*), for cardiac death (*B*), and for readmission for acute coronary syndrome (*C*) according to provocative test response. Curves are compared by the log-rank test. We had no patient loss at follow-up.

having death from any causes and in 4 of 7 (57.1%) patients having a cardiac death.

At Cox regression analysis, a positive test response [hazard ratio (HR) 7.29, 95% confidence interval (CI) 1.63–32.58; $P = 0.009$] and CCB dose reduction or discontinuation at follow-up (HR 4.28, 95% CI 1.48–12.36; $P = 0.007$) were significant predictors of all-cause death (see Supplementary material online, *Table S3*). Of note, no difference existed in the prediction of adverse events between ACh or ergonovine provocative test. Importantly, no HR of positive vs. negative provocative test could be calculated for cardiac death, as this endpoint did not occur in any patient with negative test.

At multivariable Cox regression including a positive test response and CCB dose reduction or discontinuation at follow-up, only a positive test response was independently associated with death from any

Table 2 Clinical outcomes of overall population and according to invasive provocative test response

	Total population (*n* = 80)	Positive functional test (*n* = 37)	Negative functional test (*n* = 43)	*P*-value
Death from any causes, *n* (%)	14 (19.7)	12 (32.4)	2 (4.7)	0.002
Cardiac death, *n* (%)	7 (9.4)	7 (18.9)	0 (0)	0.005
Recurrence of acute coronary syndrome, *n* (%)	13 (17.5)	10 (27.0)	3 (7.0)	0.015
Seattle Angina Score (*n*), median (range)	100.0 (33.0–100.0)	88.0 (33.0–100.0)	100.0 (44.0–100.0)	0.001
Median follow-up time (months), median (range)	36.0 (12.0–60.0)	24.0 (12.0–60.0)	36.0 (12.0–60.0)	0.49

Table 3 Causes of death in the overall population and according to provocative test response

	Total population (*n* = 14)	Positive functional test (*n* = 12)	Negative functional test (*n* = 2)
Cardiac causes, *n* (%)			
Cardiac arrest	5 (35.7)	5 (41.7)	0 (0.0)
Ventricular tachycardia/fibrillation	3 (21.4)	3 (25.0)	0 (0.0)
Bradycardia/asystole	2 (14.3)	2 (16.7)	0 (0.0)
Acute myocardial infarction	2 (14.3)	2 (16.7)	0 (0.0)
Non-cardiac causes, *n* (%)			
Cancer	3 (21.4)	2 (16.7)	1 (50.0)
Haemorrhage	1 (7.1)	1 (8.3)	0 (0.0)
Infection	1 (7.1)	1 (8.3)	0 (0.0)
Pulmonary embolism	1 (7.1)	1 (8.3)	0 (0.0)
Unknown	1 (7.1)	0 (0.0)	1 (50.0)

causes (HR 5.37, 95% CI 1.15–25.20; $P = 0.033$) (see Supplementary material online, *Table S4*).

Finally, comparisons of the Kaplan–Meier curves by log-rank test showed that patients with positive provocative test had a worse survival compared to those with a negative test in terms of death from any cause ($P = 0.002$), cardiac death ($P = 0.005$), and readmission for ACS ($P = 0.015$) (*Figure 2*). Causes of death in the overall population and according to provocative test response are listed in *Table 3*.

Clinical outcome according to occurrence of epicardial or microvascular coronary spasm

Among patients with a positive test, epicardial spasm was detected in 24 (64.9%) patients and microvascular spasm in 13 (35.1%) patients. Clinical and angiographic characteristics were not different between patients presenting with epicardial or microvascular spasm during provocative test. However, among patients with a positive test, clinical outcome was significantly worse in patients with epicardial spasm compared to patients with microvascular spasm. In particular, patients with epicardial spasm presented a significantly higher rate of death from any cause [11 (45.8%) vs. 1 (7.7%); $P = 0.027$] and a numerically higher rate of cardiac death [6 (25.0%) vs. 1 (7.7%), $P = 0.38$] compared to patients with microvascular spasm. Rates of readmission for ACS were similar [7 (29.2%) vs. 3 (23.1%), $P = 0.72$]. Of importance, patients with epicardial spasm had a worse angina at 1 year status as assessed by SAQ [Seattle score: 52.5 (33.0–100.0) vs. 100.0 (66.0–100.0); $P = 0.001$] compared to patients with microvascular spasm.

Discussion

Our study represents the first study evaluating the safety and the prognostic value of provocative tests in patients presenting with MINOCA and suspected coronary vasomotor abnormalities. In particular, in our study, we enrolled patients with MINOCA after exclusion, based on a careful clinical assessment, of aetiologies like takotsubo disease, myocarditis, coronary embolization, or type 2 MI caused by extracoronary causes. Of importance, we demonstrated that in this selected subset of patients, a positive provocative test is safe and portends a worse prognosis with regard to both hard clinical endpoints (death from any cause, cardiac death, readmission for recurrent ACS) and quality of life (worse angina status) (*Figure 3*). However, it should be underscored that the negative prognostic value of positive provocative tests was mainly related to the induction of epicardial spasm. Accordingly, a CCB dose reduction or discontinuation was associated with mortality, supporting the crucial role of epicardial spasm in the occurrence of fatal events in our patients. On the other hand, our data could not definitely demonstrate an increased rate of fatal events in patients with induction of coronary

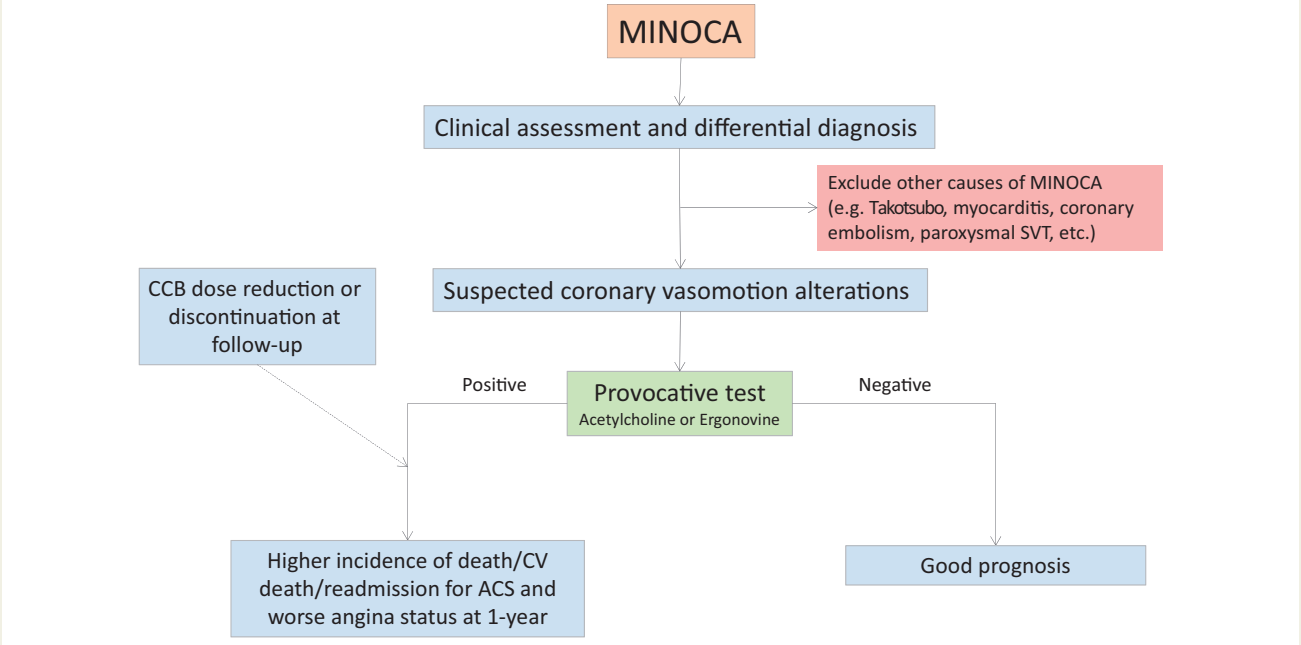

Figure 3 Clinical relevance of provocative test in patients presenting with myocardial infarction and non-obstructive coronary arteries and suspected coronary vasomotion alterations. ACS, acute coronary syndrome; CCB, calcium channel blockers; CV, cardiovascular; MINOCA, myocardial infarction and non-obstructive coronary arteries; SVT, supraventricular tachycardia.

microvascular spasm; the number of patients with microvascular spasm in this study was low, however, suggesting that this aspect should be investigated in larger studies.

Because coronary spasm is a transient functional abnormality, its documentation during daily life is elusive; thus, spasm provocation plays a key role for its diagnosis. The safety of spasm provocation tests remains a major concern and provocation tests are not included in the diagnostic algorithms of current guidelines for patients presenting with ACS. Indeed, provocation tests are thought to have a potential risk of arrhythmic complications including ventricular tachycardia, ventricular fibrillation, and brady arrhythmias. However, recent studies demonstrated the safety of provocative tests in large cohorts of patients with suspected angina.[24,25] In our study, we demonstrated for the first time the safety of provocative tests also in patients presenting with MINOCA and suspected vasomotion abnormalities.

Previous published studies demonstrated conflicting data regarding the prognostic value of provocative tests in the setting of patients presenting with an ACS and unobstructed coronary arteries. In particular, the CASPAR study[16] showed an excellent prognosis for survival and coronary events at 3 years of follow-up among 76 patients with an acute coronary presentation, non-obstructive coronary arteries, and a positive provocative test. However, as suggested by the authors, the favourable outcome in this study may probably be related to the fact that 91% of their patients presented with unstable angina without troponin elevation. Similarly, Wang *et al.*[17] showed a good outcome regarding cardiac death in their 93 Japanese patients with an acute coronary presentation, non-obstructive coronary arteries, and a positive provocative, but again the majority of patients (75%) had unstable angina. A recently published multicentre registry of the Japanese Coronary Spasm Association[24] enrolling 1244 patients with positive provocative test (7% of patients only with MI) demonstrated that, at a median follow-up period of 32 months, 69 (5.5%) patients reached the primary endpoint, including cardiac death in 4, non-fatal MI in 7, hospitalization due to unstable angina in 55, and heart failure in 3. Moreover, appropriate implantable cardiac defibrillator (ICD) shocks for ventricular fibrillation were documented in 2 of the 14 out-of-hospital cardiac arrest survivors with ICD.

In our study, despite all patients with a positive test were discharged on CCB up-titrated at the highest tolerated dose, their clinical outcome was unfavourable. Multiple mechanisms may explain these findings. First, it is well known that medical therapy in patients with vasospastic angina has some limitation, with a sizeable proportion of patients presenting angina refractory to medical treatment.[26–28] Second, adverse effects due to higher doses of or different combinations of agents may lead to therapy being discontinued or down-titrated, and this is a common issue in patients with vasospastic angina.[28] Of importance, in our study, ~40% of patients with a positive test response had a CCB dose reduction or discontinuation at follow-up, and two-thirds of deaths from any causes and ~60% of cardiac deaths among patients with a positive provocative test occurred in patients having a CCB down-titration. Third, our study cohort included only patients presenting with an acute MI, probably presenting a more aggressive form of vasospastic angina possibly potentiated by the inflammatory response triggered by myocardial necrosis.[29,30] Accordingly, in a study by Wakabayashi *et al.*[31] among patients admitted with MI, obstructive coronary atherosclerosis treated with urgent percutaneous coronary intervention those who had a positive response to ACh 10–20 days after the index event had a worse

outcome than patients with a negative response. In particular, major adverse cardiac events (death, ACS, or revascularization) occurred in 47.1% of patients with a positive response and in 27.3% of those with a negative response. Furthermore, provoked coronary spasm was a significant independent predictor of a worse outcome. Of importance, this is the first study enrolling a selected population of patients presenting with MINOCA and vasomotor abnormalities, and this may explain the higher rate of clinical events compared with previous studies enrolling patients with variant angina and a low prevalence of MI.[16,17]

In our study, patients with epicardial spasm had a higher rate of clinical events compared with patients with microvascular spasm. Our results are at variance with those of Lee *et al.*[32] showing a similar good prognosis in patients with epicardial spasm and those with microvascular spasm. However, this study was focused on patients with rest angina while our study enrolled only patients with MINOCA.

In our study, 46.2% of patients with MINOCA and suspected vasomotion alterations had a positive response to a provocative test. At the same time, the ACOVA study evaluating patient with stable angina and normal coronary arteries reported a rate of 62% positive ACh test response.[33] These data underline the importance of performing a provocative test to get a diagnosis in both MINOCA and stable angina with normal coronary arteries. Interestingly, our study showed that the prevalence of a positive response to provocative testing was higher among patients with non-obstructive coronary atherosclerosis as compared to patients with angiographically normal coronary arteries in keeping with previous observations.[24,34]

Previous reports showed a link between MINOCA and female gender.[3] In contrast, our study demonstrated that the occurrence of MINOCA with suspected coronary vasomotor abnormalities is similar among male and female, probably suggesting that only specific aetiologies of MINOCA (e.g. takotsubo disease) may be gender dependent. In line with our data, a recent systematic review of studies enrolling patients with MINOCA demonstrated that only 40% of patients were female.[35]

Limitations

Our study has some limitations. First, it is a single-centre study. Second, the study population is not large. Third, the optimal test to be used (either ergonovine or ACh) cannot be deduced by our results. In our institution, as each operator is familiar with a particular vasoactive drug, the choice of the vasoactive drug was left to physician's discretion to facilitate enrolment process. However, the use of two different drugs, with two different mechanisms of action, to induce coronary spasm may be another limitation of our study. Moreover, we did not measure coronary flow reserve and, therefore, its potential relationship with the response to vasoconstrictor stimuli. Only ~60% of our patients with a positive provocative test response were discharged on statin therapy; however, the prescription of statins at discharge did not predict the occurrence of death in this study. Finally, we did not perform a cardiac magnetic resonance imaging in the patients enrolled in the study, and so, we cannot exclude that in some of them the underlying cause of MINOCA was myocarditis; indeed, it has previously been observed that ACh testing is positive in some of these patients.[36]

Conclusion

In conclusion, this study shows for the first time that among patients with MINOCA, after exclusion of other aetiologies such as myocarditis, takotsubo disease, or coronary thrombo-embolism, provocative testing with ACh or ergonovine is safe and identifies a subset of patients with a poor outcome. It remains to establish what is the most appropriate form of follow-up and treatment to improve the outcome in these patients. Further larger studies are warranted in this patient population in the attempt to improve the outcome.

Supplementary material

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

Conflict of interest: none declared.

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