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DOCTORAL DISSERTATION

Characteristics and prognosis of patients with acute myocardial infarction in the absence of obstructive coronary artery disease (MINOCA)

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SUMMARY

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PART I

INTRODUCTION

1.1 Background

The observation that coronary artery obstruction plays a pivotal role in the pathophysiology of MI was first reported in English in 1912 by James Herrick.[1] However, it was not until the 1980s, that this phenomenon was systematically analysed.[2,3] In patients undergoing coronary arteriography within the first few hours of a transmural or non-transmural MI, the authors found a very high prevalence of obstructive atherosclerosis in both conditions, with a remarkable prevalence of total coronary occlusion in patients with transmural Mis.[2,3]

Nonetheless, even in these pioneristic study it was early recognized that in a substantial minority of patients undergoing coronary angiography with a clinical picture consistent with a MI, no significant coronary artery stenosis can be found. In the past, these patients were considered to have a "false positive" MI diagnosis.[4]

However, in 2013, John F Beltrame coined the name MINOCA, an acronym to indicate myocardial infarction and nonobstructed coronary arteries.[5]

The introduction of this new concept was meant to fill a gap in our knowledge and to encourage discovery of putative pathophysiological mechanisms. In the last few years, the new MINOCA concept has given fresh impetus to basic and clinical research in the whole field of acute coronary syndromes.

1.2 Definition of MINOCA

In 2016, an ESC working group developed the first international consensus document on this topic, in which MINOCA was diagnosed by the evidence of acute MI defined by detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile of upper reference limit and angiographic documentation of coronary stenosis <50% in any potential infarct related artery (IRA) (Table 1).[6]

Moreover, the IV Universal Definition of MI clearly stated that MINOCA is diagnosed when there is evidence of ischemia at clinical, electrocardiographic and /or imaging examination, in order to distinguish an acute MI from other causes of acute myocardial injury, as myocarditis or Takotsubo syndrome which are well distinct and specific conditions.[7-9]

Therefore, the approach to MINOCA should be that of "a working diagnosis",[6] where coronary angiography is just the first step.

1.3 Epidemiology

The ascertainment of MINOCA's prevalence has been complicated by a substantial heterogeneity in the definition of obstructive CAD in published reports. MINOCA could represents 2 to 6% of all MIs.[10,11] Furthermore, the male/female imbalance seen in MI due to obstructive CAD (MI-CAD) is far less pronounced in MINOCA, as it affects women up to 50% of cases and more often in pre-menopause period.[10,12] The mean age is 55 to 65 years, slightly lower than that of patients with obstructive CAD.[12,13]

MINOCA is more frequent in black, Hispanic, Maori and Pacific ethnic groups, which are usually underrepresented in clinical studies.[12]

The prevalence of traditional cardiovascular risk factors appears to be lower among MINOCA than among MI-CAD patients.[10,12] Although rare, hypercoagulable states are found more frequently in MINOCA than in MI-CAD.[10,12]

Finally, the ECG presentation can be that of a ST elevation MI (STEMI) in up to one third of cases. Nonetheless, troponin elevations appears to be less pronounced in MINOCA than in MI-CAD.[10,12]

1.4 Physiopathology and Classification

MINOCA encompasses a wide spectrum of conditions. Recognition of pathophysiological mechanisms behind each of these clinical entities is key to successful patients' management. According to the IV universal definition of MI,[7] MINOCA could be classified in 3 categories: type 1 MINOCA, type 2 MINOCA and type 3 MINOCA (Figure 1).

1.4.1 Type 1 MINOCA

The main feature of type 1 MI is the presence of atherothrombosis secondary to plaque disruption,[7] which encompasses plaque rupture (PR), plaque erosion (PE) and calcified nodule (CN).[14]

PR is defined by the presence of fibrous cap discontinuity with a cavity formation within the plaque.[14] PE is defined by mural thrombosis associated with no evidence of plaque rupture.[14] CN is a less frequent condition in which there is disruption of the fibrous cap overlying or close to a calcified plaque with protruding calcification.[14]

Diagnosis of plaque disruption could be challenging based solely on coronary angiography and can be achieved by intracoronary imaging.[14,15]

According to intravascular ultrasound (IVUS) studies, atherosclerotic plaque disruption with superimposed thrombosis is identifiable in approximately one third of MINOCA patients.[15]

Optical coherence tomography (OCT) is more sensitive than IVUS to identify coronary wall anomalies and thrombus, in fact in a recent study plaque disruption was found in 42% of MINOCA patients, also with good agreement between OCT findings and presence/location of signs of ischemic myocardial injury at CMR.[16]

There are several putative mechanisms by which plaque disruption may provoke a MINOCA. Among them, distal embolization, spontaneous thrombus recanalization or superimposed spasm seem most likely.[7]

1.4.2 Type 2 MINOCA

Type 2 MINOCA is defined by the presence of MI secondary to myocardial oxygen supply/ demand imbalance in the absence of acute atherothrombosis and/or plaque disruption.[7] As in type 1 MINOCA the presence of ischemia and stenosis <50% are required for diagnosis.[7] Type 2 MINOCA can be secondary to coronary and noncoronary causes, as listed:

1) Coronary causes: coronary spasm, coronary microvascular disfunction; spontaneous coronary artery dissection (SCAD) and/or intramural haematoma, coronary embolism;

2) Non-coronary causes: severe tachy- or bradyarrhythmias; severe hypertension or hypotension; presence of left ventricular hypertrophy (LVH); severe anemia; hypotension/shock; severe hypoxia or respiratory failure.

1.4.2.1 Coronary spasm

Coronary artery spasm is identifiable as causative mechanism of MINOCA in more than 40% of cases.[17]

East Asians seem to be particularly prone to this condition.[18]

Coronary artery spasm is defined as a marked focal or diffuse reduction in epicardial coronary artery's calibre. Spasm episodes can either be spontaneous or provoked by chemical triggers, such as cocaine or 5-fluorouracil. When severe and prolonged, coronary artery spasms can lead to a MI[18]. Interestingly, animal models have shown that there is a topological correspondence between spasm and atherosclerotic lesions. Nonetheless, atherosclerotic stenoses are not a necessary prerequisite for spasm, which can occur in angiographically non-stenosed or even smooth arteries.

Occasionally, spontaneous spasm can be identified on coronary angiography. More commonly, spasm can be elicited by means of provocative tests.[18] Nowadays, the preferred method involves intracoronary acetylcholine infusion at increasing doses, evaluating patient's clinical, electrocardiographic and angiographic response.[18] Despite rarely performed out of fear of complications, provocative tests are safe, with a reported rate of significant arrhythmias of 1% when

performed on stable patients.[19] Furthermore, most complications can be successfully managed by pre-emptively positioning a temporary pacemaker or by administering intracoronary nitrates.[18,19]

The only pilot study in which provocative tests were performed in MINOCA patients within 48 hours of admission included 80 patients. Interestingly, the tests enabled identification of epicardial coronary artery spasm and microvascular spasm in 30% and 16% of patients, respectively. Patients with a positive test had a greater risk of long-term cardiovascular events or death, and no adverse events were reported.[17]

Therefore, provocative testing could have an important diagnostic and prognostic yield, while being overall safe.[18]

1.4.2.2 Coronary microvascular disfuntion

A landmark study including nearly 400000 patients undergoing coronary angiography, 84% of whom had a positive non-invasive test, showed that almost 60% of patients had no coronary stenosis ≥50%.[20] The majority of these patients were discharged with a diagnosis of non-cardiac chest pain. Nonetheless, objective evidence of coronary microvascular dysfunction (MD) can be found in approximately one half of similar subjects.[21]

The term impaired coronary microvascular function should be used to indicate either a reduction in coronary flow reserve (CFR) in the absence of obstructive epicardial CAD or coronary microvascular spasm or the coronary slow-flow phenomenon.[22,23] CFR is the ratio of maximal coronary flow over basal state flow, and it should be considered diagnostic of MD when it is less than two.[23]

MD should be suspected when there is a history of effort or rest angina, objective evidence of myocardial ischemia on ECG stress testing, absence of significant coronary obstruction (defined as stenosis ≥50% on angiography or fractional flow reserve <0.8) .[23]

Although the relationship between MD and MINOCA is complex, impaired microvascular function seems to be a possible cause of MI per se. The main presumed mechanism is a prolonged and intense microvascular spasm.[7]

1.4.2.3 Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is an important and often overlooked condition which could represent a cause of MINOCA.[24]

SCAD is defined as an intramural hematoma occurring in the tunica media, not associated with trauma, atherosclerosis or medical interventions.[25] When SCAD determines a critical limitation of coronary blood flow, MI ensues.

Two different mechanisms have been proposed to explain SCAD, according to the primary event. According to the first one, intimal rupture provokes extravasation of blood into the medial layer, forming a false lumen which can potentially compress the true coronary artery lumen. The second hypothesis postulates that haemorrhage in the tunica media is the inciting event and intimal rupture may be a secondary phenomenon related to the increased pressure in the false lumen.[26]

SCAD's multifactorial pathophysiology seems dependent on a both a predisposing substrate that weakens the coronary artery wall (such as fibromuscular dysplasia, hormonal factors in pregnancy, inflammatory conditions or genetic syndromes such as Marfan, vascular Ehler-Danlos or Loeys-Dietz) and a triggering event, most commonly extreme physical or emotional stress.[26]

Although initially presumed a rare and fatal cause of peripartum MIs, contemporary series report that 1 to 4% of MIs are caused by SCAD. Women of reproductive age are primarily affected: almost 35% of MI in women ≤50 years of age are due to SCAD[25,26] and SCAD is the most common cause of MI in pregnancy.[27]

Even in this case, coronary angiography is key. SCAD's classic appearance includes multiple radiolucent lumens and extraluminal contrast staining. However, this angiographic presentation can

be currently found only in a minority of cases,and sometimes SCAD could mimic a coronary atherosclerotic plaque.[28]

In subtle or uncertain cases, diagnosis should be confirmed by means of intracoronary imaging.[26] OCT is the preferred imaging modality over IVUS, because it allows a clearer visualization of lumen-intimal interface and intramural hematoma.[29]

Given that obstruction of a coronary artery's lumen is not prerequisite for SCAD diagnosis and that angiographic appearance can be inapparent,, a considerable yet underestimated proportion of MINOCAs may be due to SCAD. Moreover, overlooking of SCAD could also be provoked by contrast medium flush which can contribute to reduce false lumen by increasing pressure in the true lumen at the time of angiography, thus challenging the diagnosis of SCAD in absence of intracoronary imaging. Hopefully, the increasing use of intracoronary imaging modalities, especially OCT, will lead to improved diagnostic capabilities.[24,26]

1.4.2.4 Coronary embolism

Coronary thrombosis can occur in intact coronary vessels as a result of a genetic or acquired thrombophilia. With regard to the former, a systematic review found that as many as 14% of MINOCA patients had a hereditary thrombophilia, most commonly the Leiden factor V mutation.[10] Reported risk of MINOCA among subjects with this genetic variant ranges from 1.3% to 3.7.[30,31] Other predisposing causes of coronary embolism include atrial fibrillation and other causes of dislodgement of non-thrombotic material, such as endocarditis or cardiac neoplasia.[6] If clinical context is unclear, it is reasonable to exclude pulmonary embolism which could be a cause ot cardiac troponin rise.[6,12]

Testings for genetic or acquired thrombophilia, are of unclear significance, and should be performed in consultation with a haematologist.[12]

1.4.2.5 Non-coronary causes of type 2 MINOCA

Supply-demand mismatch is important cause of MINOCA. When the decrease in coronary blood flow and/or the increase in myocardial oxygen demand are not due to coronary atherosclerotic plaque disruption and are severe enough to provoke myocardial cell ischemic death, a type 2 MI will ensue.[32] In this process, non-obstructive atherosclerosis may act as a modulating factor of the ischemic threshold. MINOCA is not synonym for type 2 MI, since a considerable proportion of MINOCAs are related to coronary atherothrombosis.[12,16]

Supply-demand mismatch related MINOCAs make a broad category, which includes some of the aforementioned mechanisms, such as epicardial coronary artery spasm, impaired coronary microvascular function, SCAD or coronary embolism. Furthermore, especially among critically ill and old patients, non-coronary conditions as anemia, severe hypoxia, hypotension/shock, hypertension with or without LVH, sustained tachy- or bradi-arrhythmias may be important elements precipitating the ischemic imbalance. Most of these conditions simultaneously reduce coronary perfusion and increase myocardial oxygen requirements.[32]

1.4.3 Type 3 MINOCA

Type 3 MI is defined as the occurrence of sudden cardiac death (SCD) , in a clinical scenario suggestive of myocardial ischemia (symptoms, ECG changes), just before biomarkers can be obtained, or before increases in cardiac biomarkers can be observed, or when MI is detected by autopsy examination. Also in this case presence of coronary stenosis <50% is required for diagnosis of type 3 MINOCA.[7] There are very few autopsy data regarding patients affected by SCD and with a histological diagnosis of MI in absence of coronary alterations, but drugs and illicit substance misuse appears to be highly prevalent in this population.[33] Of note, if recent thrombus in the infarct-related artery is found at autopsy, the type 3 MI should be reclassified to a type 1 MI.[7]

1.5 Diagnosis

As clearly pointed out in a recent Scientific Statement from the American Heart Association, clinical judgment should guide clinicians through the "traffic-light" sequence for MINOCA diagnosis.[12] Several key-points deserve a special mention.

Diagnosing ischemia is the first step over a correct MI diagnosis. In addition to the clinical context and electrocardiographic changes, cardiac magnetic resonance (CMR) is an important tool. In fact, contrast CMR can detect even subtle signs of a MI (CMR-confirmed MINOCA), or show suggestive evidence of myocarditis or other cardiomyopathies.[10,34] However, as CMR is not available in every clinical contest, diagnosis of MINOCA should be also made without ("not CMR-confirmed MINOCA").[12]

Intracoronary imaging as OCT and IVUS should be considered in order to rule-out plaque disruption and SCAD.[12]

Of note, the presence of coronary stenoses ≥ 30% and < 50%, has been defined "mild coronary atheromasia" (MCA),[6] and may be relevant for prognosis among MINOCA patients, especially if MCA involves all 3 major coronary vessels and/or left main (LM).[11]

Of interest, in a recent study by Montone et al., it has been demonstrated that if FFR was performed in MINOCA patients with evidence of MCA, in over 90%% of cases the result was < 0.8, thus allowing re-classification as MI-CAD.[17]

Furthermore, provocative spasm testing with acetylcholine should be considered, given its safety and high diagnostic yield.[11,35]

The role of thrombophilia screening is uncertain and should be performed in consultation with a haematologist[12] (table 2).

1.6 Prognosis

Unlike the classic perception, there's a mounting evidence that MINOCAs' prognosis is not completely benign[10]. Data from a large number of patients from different studies reveal an all-cause in-hospital and 12-month mortality of 0.9% and 4.7%, respectively.[10] These numbers indicate a lower yet still considerable risk when compared to MI-CAD.[10]

In addition, several clinical and angiographic features have reported has independent predictor of adverse outcome: C-reactive protein,[11] MCA involvement of 3-vessels and/or LM,[11] atypical symptoms,[36] ST-elevation or Killip class IV at admission,[36] diabetes,[36] provoked coronary spasm.[17]

However, many studies are biased by use of administrative data and considering MINOCA also patients with cardiomyopathies, myocarditis, Takotsubo syndrome and extra-cardiac severe diseases, thus these data on prognosis should be considered with caution[10,37].

1.7 Therapy

As MINOCA is not a single entity but a heterogeneous group of different clinical conditions, the therapeutic approach should address the specific mechanisms underlying clinical presentation. However, some general considerations can be applied to MINOCA's secondary prevention.

1.7.1 Antithrombotic therapy

For patients with type 1 MINOCA, antithrombotic agents should be considered.. However, as there are no specific studies, this hypothesis is the results of translation of evidence from MI-CAD secondary prevention trials results, in which antithrombotic therapy was administered even in absence of coronary angiography.[38,39]. In these studies, clopidogrel consistently proved beneficial in terms of hard clinical endpoints, such as death and MI recurrence.[38,39] In a recent Swedish study

DAPT had a neutral effect on outcome of MINOCA patients,[13] although this population was highly heterogeneous thus probably including many cases of myocarditis and Takotsubo syndrome.[40] There are no specific study addressing use of anticoagulants in MINOCA.

1.7.2 Beta-blockers

The use of beta-blockers has been reported to reduce recurrences among patients affected by SCAD,[41] with a not significant benefit trend reported in the previous reported Swedish study.[13] Caution should be used in case of proven vasospastic aetiology, although selective beta-blockers could be considered when there is a fixed component of coronary obstruction in addition to dynamic spasm.[23]

1.7.3 Statins

Statins were shown to have long term beneficial effect among over 9000 MINOCA patients,[13] thus should be considered especially in type 1 MINOCA,

1.7.4 Renin-angiotensin-aldosterone system modulators

Agents modulating the renin-angiotensin-aldosterone (RAA) system are well known to have significant cardioprotective effect in many subset (guidelines HF and secondary prevention).
IN the study by Lindahl et al. ACE/ARB were significantly effective to improve prognosis in patients with MINOCA.[13] There are no high quality data on MRA, which could be reserved to patients with MINOCA and reduced left ventricular ejection fraction.

1.7.5 Calcium-channel blockers and other vasodilators

When epicardial coronary artery spasm is identified, calcium channel blockers are a first line option, not only because of their effectiveness in symptoms control, but also because they are positively related to long term prognosis.[42] Among calcium channel blockers, both dihydropyridine

and non-dihydropyridine agents proved to be effective.[42] Nitrates are usually prescribed for long term symptoms control as an adjunct to calcium-channel blockers, although their prognostic role is uncertatin.[43]

Other vasodilating agents with proven effectiveness for coronary artery spasm include nicorandil, cilostazol, fasudil.[42]

1.7.6 General measures

It seems reasonable that cardiovascular risk factors should be adequately managed in these patients. Avoidance of triggers, such as smoking, cocaine, serotoninergic or ergot compounds, and even chemotherapeutic agents such as 5-fluorouracil, capecitabine and sorafenib, which can all cause coronary vasospasm.[42]

In case of coronary microvascular disfunction, there are limited data on the use of calcium channel blockers, beta-blockers, statins, enalapril, ranolazine, dipyridamole, which might all improve coronary microvascular flow by different mechanisms and thus alleviate anginal symptoms.[22]

When clinical presentation is consistent with a supply-demand mismatch, inciting factors (i.e., tachyarrhythmia, hypoxemia, anaemia, hypertension) should be promptly identified and corrected. Antithrombotic agents have little or no role in this condition.[32] However, high-quality data from prospective, randomized controlled trials are still lacking.

1.8 Controversial aspects

There some issues that should be addressed. First, arbitrary cut-off of 50% could be arguable, as a stenosis of 40% in the left main stem probably has not the same prognostic value than in another coronary artery. Second, a priori exlusion of confounding diseases as myocarditis and Takotsubo syndrome should be required from studies which address MINOCA. Third, the role of pharmacological therapy as secondary prevention remains unclear. Fourth, in order to assess the

prognostic role of MINOCA, studies aimed to explore the correlation of this condition with sudden cardiac death should be encouraged.

Interest around MINOCA has greatly grown in the past 6 years. Advanced diagnostic tools, such as cardiac MRI, intracoronary imaging and provocative tests should be considere after coronary angiography among these patients. These exams allow identification of pathophysiological mechanisms, which can be targeted by specific treatments. Nonetheless, future research will need to unravel new mechanistic insights and develop new therapeutic measures, in order to improve the patients' prognosis.

1.9 References

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1.10 Tables and figures

Table 1

Diagnostic criteria for MINOCA (adapted from Agewall S et al. and Tamis-Holland J et al.)

Acute myocardial infarction according to the "Fourth Universal definition of myocardial infarction

• Positive cardiac biomarker (preferably troponin): detection of rise and/or fall in serial levels, with at least one value above the 99th percentile upper reference limit
• Corroborative clinical evidence of infarction as evidenced by at least one of the following:
  • Symptoms of ischaemia
  • New or presumed new significant ST-T changes or new LBBB
  • Development of pathological Q waves
  • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  • Intracoronary thrombus evident on angiography or at autopsy

Non-obstructive coronary lesions on angiography
• Absence of any coronary artery stenosis ≥ 50% in any infarct related artery This includes both patients with: • Normal coronary arteries ("smooth coronary arteries") • Mild luminal irregularities (no angiographic stenosis > 30%) • Moderate coronary atheromatosis (stenosis > 30% but < 50%)
No clinically overt specific cause for the acute presentation

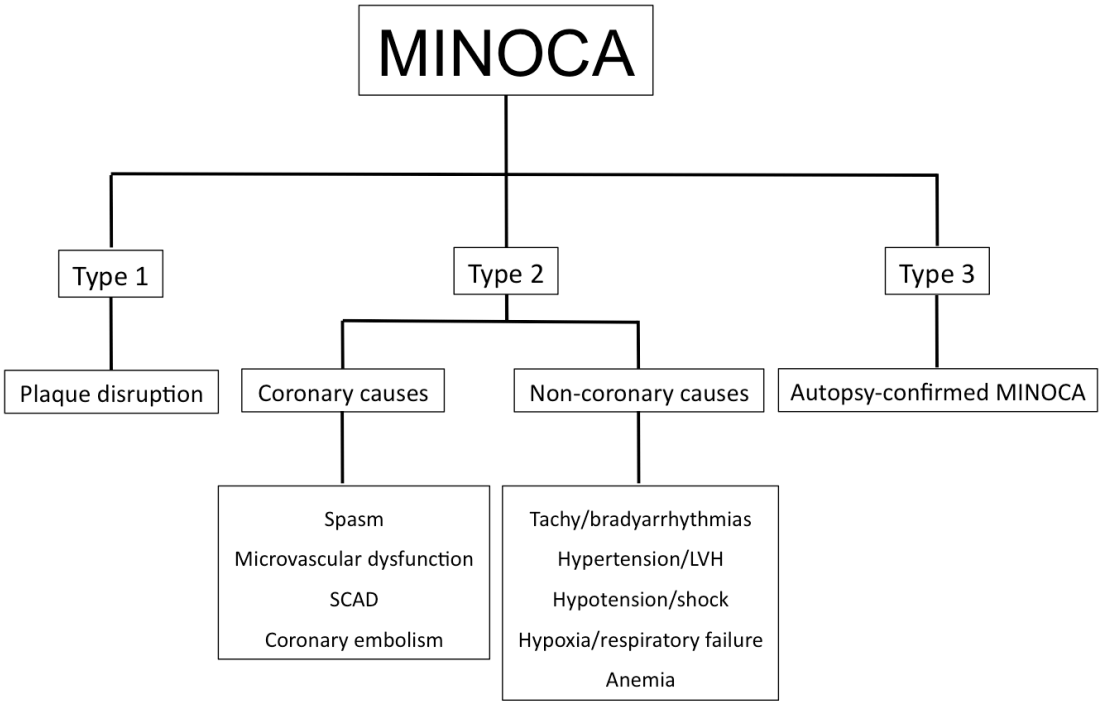
Table 2

Management approach to MINOCA according to the IV Universal Definition of myocardial infarction.

	DIAGNOSIS	THERAPY
Type 1 MINOCA	Angiographic Review OCT IVUS	Aspirin P2Y12 inhibitors Statin ACE inhibitors-ARBs Beta-blocker
Type 2 MINOCA	• **Spasm:** Angiographic Review Provocative Spasm Testing Blood Toxicology Testing • **Microvascular Dysfunction** Angiographic Review Provocative Spasm Testing • **SCAD** Angiographic Review OCT IVUS • **Coronary Embolism** Angiographic Review OCT IVUS Thrombophilia Screening • **Non Coronary Causes** Vital Signs CBC BGA	• **Spasm** Calcium Channel Blockers Nitrates Nicorandil, Cilostazol, Fasudil • **Microvascular Dysfunction** Calcium Channel Blockers Beta Blockers Other Therapies: Statins, Enalapril, Ranolazine, Dypiridamole • **SCAD** Aspirin Beta Blockers Clopidogrel • **Coronary Embolism** Aspirin Clopidogrel/Ticagrelor Anticoagulants • **Non Coronary Causes** Treatment according to the identified cause (anti-hypertensive drugs, beta-blockers, fluids, transfusions, oxygen)

Figure 1

Classification of MINOCA according to the IV Universal Definition of myocardial infarction.



PART II

CHARACTERISTICS AND PROGNOSIS

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1. Aims and Methods

Little is known about the prognosis of MINOCA as few studies have assessed clinical outcome and most of them have included patients with myocarditis and patients with Takotsubo syndrome [1-5]. Moreover, even less prognostic information is available on patients with MINOCA whose etiologic diagnosis remains undefined ("idiopathic" MINOCA), which account for at least 20-25% of MINOCA patients [3,4]. In a recent Position Paper of the European Society of Cardiology (ESC) [5], the following criteria for diagnosis of MINOCA were proposed: 1) AMI according to the III universal definition of AMI [6]; 2) absence of ≥50% stenosis at angiography; 3) exclusion of other clinically overt specific etiologies. The authors subdivided MINOCA patients in two groups: a) normal coronary arteries (stenosis <30%); b) mild coronary atheromatosis (stenosis ≥ 30% but <50%).

The aim of this study is to assess the characteristics and the long-term prognosis of a contemporary cohort of patients with MINOCA.

1.1 Patient recruitment

The study cohort was derived from 7935 consecutive patients discharged from hospital with the diagnosis of AMI and who were systematically entered in the AMI registry of the Cardiology Department of Perugia University Hospital from 1th January 2006 to 31th December 2014. Patients were identified as having AMI according to the International Classification of Diseases, 10th Revision (ICD-10) codes: I21-I22-I23. We retrospectively analysed this source and selected patients with: (I) diagnosis of AMI; (II) coronary angiography within 48 hours from onset of symptoms; (III) absence of ≥50% coronary stenosis. Following the publication of the III universal definition of AMI, all patients in the database were reclassified in accordance with this definition [6]. 150 patients satisfied all selection criteria and were included in the study (Figure 1). Follow-up

was carried out at regular outpatient visits and/or by telephone contact. Full follow-up data were available for 132 patients (88%). The study was approved by the local ethics committee and managed in accordance with Good Clinical Practice and the Declaration of Helsinki [7].

1.2 Data collection

Two researchers (G.C. and M.B.) independently double checked the information available on the database and when discrepancies arose these were discussed with a third senior researcher (I.T.) and sorted out by consensus. The following clinical variables were collected and assessed: a) medical history including hypertension, diabetes mellitus, hyperlipidaemia, smoking and CAD family history, presence of atrial fibrillation, chronic obstructive pulmonary disease (COPD), cerebrovascular disease and prior AMI; b) body mass index (BMI), systolic blood pressure and heart rate at admission; c) ECG, left ventricular ejection fraction (LVEF) at admission; d) blood test results including cardiac troponin and CK-MB peak concentrations, creatinine, haemoglobin, white blood cell count, C-reactive protein (CRP) and uric acid levels.

Patients were subdivided into two groups according to the extent of their CAD, as proposed by the recent ESC position paper on MINOCA [5]: patients with normal coronary arteries (NCA) (no stenosis or stenosis <30%) and patients with mild coronary artery disease (MCAD) when stenosis ≥30% but <50% were present. With regard to the distribution of CAD, patients were subdivided into 3 groups: I) 0 vessel disease (absence of stenosis ≥30%); II) 1-2 vessel disease, when MCAD was observed in 1 or 2 major coronary arteries and III) 3-vessel disease, when 3 vessels or the left main stem (LMS) showed MCAD.

1.3 Statistical analysis

Continuous variables are expressed as mean (±SD) and categorical variables as percentages. We used chi-square tests and one-way ANOVA for statistical comparisons of clinical

characteristics among groups. For the purpose of this study, the endpoint was represented by a composite of major adverse cardiovascular events (MACE) including: cardiovascular death, AMI or acute coronary syndrome (ACS), heart failure leading to hospitalization (HF), stroke. Death was considered as of cardiovascular origin unless obvious non-cardiac causes could be identified. Univariate analyses by Cox proportional hazards models were performed to assess the association between each variable (listed in Table 1) and outcome. Variables associated with the considered outcome with a P-value <0.10 were maintained in the multivariate model along with age and male sex, considered as relevant a priori. Multivariate analyses were performed using a backward-conditional selection procedure. Kaplan–Meier method was used to estimate survival probabilities for the combined endpoint. Differences between survival curves were analysed using the log-rank test. A P-value <0.05 was considered significant. Statistical analyses were performed using SPSS package version 23.0 (Chicago, IL, USA).

2. Results

Groups 1, 2 and 3 comprised 91, 45 and 14 patients, respectively. Clinical data are reported in Table 1. Hypertension (92.9% vs. 59.3%; p=0.015) and cerebrovascular disease (14.3% vs. 2.2%; p=0.028) were more frequent in group III compared with group I; family history of CAD was more frequent in group I compared with group II (14.3% vs. 2.2%; p=0.03); all other baseline characteristics were not significantly different among the 3 groups (Table 1, supplementary material).

There were no in-hospital MACE or deaths among the study patients. At follow-up (median 7.1 years, 1.5-10.4; minimum follow-up period 328 days), a total of 23 combined events had occurred (8 cardiovascular deaths, 7 AMI/ACS, 7 hospitalizations for heart failure, and 1 stroke). In group 1, 13 MACE occurred (5 cardiovascular deaths, 3 AMI/ACS, 4 hospitalizations for heart failure, and 1 stroke). In group 2, 4 MACE occurred (1 cardiovascular death, 1 AMI/ACS, 2

hospitalizations for heart failure). In group 3, 6 MACE occurred (2 cardiovascular deaths, 3 AMI/ACS, 1 hospitalization for heart failure). Rate of MACE is shown in Figure 2.

There was a non-statistically significant difference between patients who presented with STEMI and those with NSTEMI, with the latter showing more events during follow up (Log-Rank=1.530; p=0.216) (Figure 3A). Furthermore, there were no significant differences regarding MACE when patients with NCA and those with MCAD were compared (Log Rank=1.1; p=0.781) (Figure 3B).

Patients with MCAD affecting 3 vessels or the LMS (group III) had a lower event-free survival (54%± 14%) compared to patients in group I (83%±4%) and group II (90%±5%) (Log Rank= 12.383; p=0.001; Figure 3C). Furthermore, compared with group I, used as reference, group III displayed a strong association with an impaired clinical outcome (HR 3.66, 95% CI 1.40 to 9.65; P =0.009) whereas groups I and II showed similar rates for the combined study endpoint (HR 0.55, 95% CI 0.18 to 1.70; P =0.298). Moreover, as shown in Figure 3D, Kaplan-Meier survival curves revealed a poorer outcome in patients who had a CRP >2 mg/dL at admission (Log Rank= 8.908; p=0.003;).

Univariate analysis showed prior AMI, troponin peak ratio, increased CRP levels, presence of 3-vessel and LMS MCAD to be significant predictors of MACE (Table 2). Multivariate analysis showed only 3 vessels/LMS MCAD (HR 23.5, 95% CI 2.59-173.49, p=0.001) and high CRP concentrations (HR 1.47, 95% CI 1.06-2.07; P=0.005) to be independent predictors of MACE (Table 3).

3. Discussion

The present study shows that although patients with MINOCA generally have a more favourable prognosis than patients with AMI triggered by obstructive CAD, the presence of MCAD affecting 3 vessels or the LMS identifies patients with an impaired clinical outcome. Our study also supports a significant prognostic role of increased CRP concentrations at hospital admission in patients with MINOCA.

Interestingly, our findings suggest that the distribution of CAD expressed as number of coronary vessels involved rather than the degree/severity of coronary stenosis, may represent a better risk stratification strategy. Moreover, our study indicates that in MINOCA patients, an accurate assessment of the coronary angiography and the identification of the number of vessels with MCAD could have incremental prognostic value. It can be speculated that the greater the number of vessels involved, albeit without obstructive CAD, the greater the likelihood that one or more plaques can destabilize over time, particularly in the presence of high CRP concentrations [8,9], leading to an acute coronary event. We found that the presence and the distribution of atherosclerotic plaques at angiography appears to provide a better prognostic yield than the sole estimation of the degree of stenosis, probably because the former is easier to be reported and less operator-dependent (i.e. present/absent), whereas the latter is affected by more inter-operator variability. However, given the limitations of coronary angiography to identify non-obstructive plaques, other imaging modalities such as CT (computed tomography) [10,11], IVUS (intravascular ultrasound) [12], OCT (optical coherence tomography) [13], and CMR (cardiovascular magnetic resonance) [14] may offer better diagnostic and risk-stratification options.

It has been suggested that the burden of atherosclerosis is significant in patients with AMI and no obstructive CAD and this is often overlooked by conventional angiography when compared to assessment of stenosis using CT angiography (CTA) [10,11]. In MINOCA patients with documented myocardial scar tissue, as assessed by CMR, Aldrovandi et al. reported CAD -as

assessed by CTA- in 84% of cases [10]. Furthermore, Amhadi et al. showed that mortality rates in MINOCA patients were related to the type of atherosclerotic plaques i.e. calcified plaque (1.4%), mixed plaque (3.3%) and non-calcified plaque (9.6%). In a 10-year follow up study, outcomes were impaired in patients with 3-vessel disease compared with those with single-vessel disease (p <0.001) [11]. In our study, patients with 3-vessel/LMS disease had significantly worse outcomes than patients with lesser degrees of CAD. However, prognosis was similar among patients with normal coronaries and patients with MCAD affecting 1-2 vessels.

According to our data, mortality was low in MINOCA patients assessed over a median follow-up of 7 years. This could be due to the use of more strict inclusion criteria in our study and our choice to assess cardiovascular mortality only and not all-cause mortality. In a pooled analysis of 8 studies on the prognosis of MINOCA patients (including Takotsubo and myocarditis) in-hospital and 1-year all-cause mortality were 0.9%, (95% CI, 0.5% -1.3%) and 4.7% (95% CI , 2.6% -6.9%), respectively, substantially lower than in patients with obstructive CAD (in-hospital mortality 3.2%; 1-year mortality 6.7%), but still far from negligible [4] . Of importance, among our patients with MCAD affecting 3 vessels or the LMS, 7-year cardiovascular mortality was in the region of 15%. In a recent study of patients undergoing elective coronary angiography 1-year mortality was higher in patients with 3-vessel non-obstructive CAD (i.e. stenosis >20% but <70%) compared to those with no CAD (stenosis <20%) (HR 1.6; 95% CI, 1.1 – 2.5) [15]. Rossini et al. reported similar results in unselected consecutive patients presenting with ACS. There were no differences in the incidence of MACE between patients with NCA (0% stenosis) and those with mild CAD (>0% and <50% stenosis) at either 30 days (p= 0.50) or long-term follow-up (p= 0.16) [16].

However, available data are biased by a large heterogeneity in defining normal and diseased coronaries [16,17] and often patients with normal troponin or CK-MB were also included [16]. In addition the majority of this studies are affected by significant selection biases, because they are

post-hoc analysis from multicentre trials [17] or specific registries [18], whereas others enrolled only selected populations, for instance only STEMI [17] or NSTE-ACS patients [18].

Furthermore, our results may have a practical application, i.e. the high-risk group could probably benefit from standard therapy for secondary prevention as used in obstructive CAD. In fact, in a large MINOCA population from the SWEDEHEART registry, Lindhal et al.[19] demonstrated a beneficial prognostic effect of statins and ACEI/ARB. However, in the same study beta-blockers and double anti-platelet therapy did not significantly improve outcomes, probably due to the large heterogeneity of this MINOCA population [20].

3.1 Limitations of the study

Our study has some limitations. As the current definition of MINOCA requires knowledge of coronary angiographic anatomy, we enrolled only MINOCA patients who underwent coronary angiography but angiographic results were not adjudicated by a core laboratory. The decision to refer patients to angiography was part of the clinical management of patients in the institution and as such it was left to the discretion of the managing physician; this could have resulted in an underestimation of the prevalence of MINOCA in our study, as in other MINOCA studies with a retrospective enrolment design. The relatively low prevalence of MINOCA in our study compared with other reports in the literature [4, 15-18], could also be explained by our more strict inclusion and exclusion criteria. We -*a priori*- excluded patients with myocarditis and Takotsubo syndrome, as these patients were discharged from hospital with different ICD-10 codes. Moreover our detailed evaluation of individual clinical records have allowed for further exclusion of miscoded diseases.

We do not report data on CMR, endomyocardial biopsy or provocative testing to rule out coronary spasm [21] as these tests were not part of a systematic assessment protocol and such information was available in a small number of patients in our database. Our focus was on clinical variables during follow-up. However, it is conceivable that, if CMR had been systematically

performed in all MINOCA patients, some other miscoded or misdiagnosed myocarditis (not clinically suspected, as defined by ESC guidelines [22]) could have been discovered [14].

Although baseline characteristics in our patients are similar to those in other MINOCA studies [4,17], we do not report on a matched obstructive CAD control group for comparison, as it was our aim to identify markers of risk within this study population. Pharmacological therapy was left to the discretion of the managing physician and all patients were treated according to ESC guidelines. Given the small number of events in the study our conclusions should be interpreted as hypothesis generating.

4. Conclusions

MINOCA is a relatively infrequent AMI presentation compared to ACS with obstructed coronary arteries. Albeit the absence of obstructive CAD portends good long-term prognosis, the number of vessels affected by MCAD has an incremental effect on clinical outcomes. MINOCA patients with MCAD affecting 3 vessels or the LMS appear to have a guarded prognosis. Increased CRP levels also appear to have prognostic value in these patients. Prospective studies are necessary to test the hypotheses generated by our findings.

5. References

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6. Tables and figures

Table 1

Total, n	150
Demographics	
Age (±SD)	62.6±13
Female (%)	55.3
BMI (kg/m^2)	25.3±4.7
SBP (mmHg)	145.7±26.1
HR (bpm)	73.4±13.3
Medical history, %	
Hypertension	66
Diabetes mellitus	11.3
Hyperlipidaemia	26.7
Smoking	28
CAD Family history	9.8
Atrial fibrillation	9
COPD	7.3
Cerebrovascular disease (%)	4
Prior AMI (%)	4.7
ECG at admission	
ST-elevation (%)	23.3
LVEF <55% (admission)	20.7
Blood testings	
Troponin peak (ng/ml)	0.4±1.0
CK-MB peak (ng/ml)	1.7±2.8
Creatinine (mg/dl)	0.7±0.4
Haemoglobin (g/dl)	12.6±3.8
White blood cells (x10^3)	7.1±3.2
CRP (mg/dl)	1.1±2.6
Uric acid (mg/dl)	5.5±1.9
Angiographic characteristics	
NCA, n (%)	91 (61)
1-2 vessels MCAD, n (%)	45 (30)
3 vessels/LMS MCAD, n (%)	14 (9)

Baseline characteristics in the whole cohort. AMI, acute myocardial infarction; BMI, body mass index; bpm, beats per minute; CRP, C-reactive protein; SBP, systolic blood pressure; HR, heart rate; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LMS, left main stem; LVEF, left ventricular ejection fraction; MCAD, mild coronary artery disease; NCA, normal coronary arteries.

Table 2

	HR (95%CI)	P value
Demographics		
Age (per 5 years increment)	1.01 (0.87-1.18)	0.212
Male sex	0.92 (0.40-2.10)	0.848
BMI (per 5 kg/m^2 increment)	0.01 (0-34.1)	0.375
SBP (per 15 mmHg increment)	1.17 (0.95-1.45)	0.150
HR (per 10 bpm increment)	1.04 (0.77-1.40)	0.809
Medical History		
Hypertension	0.97 (0.41-2.28)	0.939
Diabetes mellitus	0.290 (0.4-2.15)	0.226
Hyperlipidaemia	1.93 (1.40-5.40)	0.22
Smoking	1.26 (0.52-3.05)	0.612
CAD Family history	0.48 (0.14-1.60)	0.23
Atrial fibrillation	0.39 (0.1-2.74)	0.346
COPD	1.88 (0.60-6.44)	0.307
Cerebrovascular disease	1.49 (0.20-11.42)	0.699
Prior AMI	3.04 (0.90-10.22)	0.073
ECG at admission		
ST-elevation	0.47 (0.14-1.60)	0.227
LVEF <55% at admission	1.02 (0.96-1.08)	0.584
Blood testings		
Troponin peak ratio (per 0.06 ng/ml increment)	0.98 (0.97-1.01)	0.098
CK-MB peak (per 10 ng/ml increment)	0.96 (0.91-1.01)	0.106
Creatinine (per 1 mg/dl increment)	0.514 (0.16-1.66)	0.267
Haemoglobin (per 1 g/dl increment)	0.99 (0.1-2.0)	0.811
White blood cells (per 1000/mm^3 increment)	1.29 (0.36-4.60)	0,695
CRP (per 1 mg/dl increment)	1.20 (0.98-1.28)	0.087
Uric acid (per 1 mg/dl increment)	0.99 (0.74-1.33)	0.962
Angiographic characteristics		
NCA	0.89 (0.39-2.03)	0.781
1-2 vessels MCAD	0.43 (0.15-1.25	0.135
3 vessels/LMS MCAD	3.05 (1.15-9.1)	0.009

Univariate analysis for the combined endpoint (Major adverse cardiovascular events [MACE]= cardiovascular death, AMI/ACS, heart failure, stroke).

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease; NCA, normal coronary arteries.

Table 3

	HR (95% CI)	P value
Age (per 5 years increment)	0.95 (0.75-1.19)	0.634
Male sex	1.70 (0.44-6.53)	0.439
Prior AMI	2.20 (0.12-14.07)	0.187
CRP (per 1 mg/dL increment)	1.47 (1.06-2.07)	0.005
Troponin peak ratio (per 0.06 ng/ml increment)	1.04 (1.01-1.07)	0.190
3 vessels/LMS MCAD	23.5 (2.59-173.49)	0.001

Multivariate Cox model analysis for the combined endpoint (Major adverse cardiovascular events [MACE]= cardiovascular death, AMI/ACS, heart failure, stroke). ACS, acute coronary syndrome; AMI, acute myocardial infarction; CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease

Figure 1. Flow diagram for the selection of patients. AMI, acute myocardial infarction.

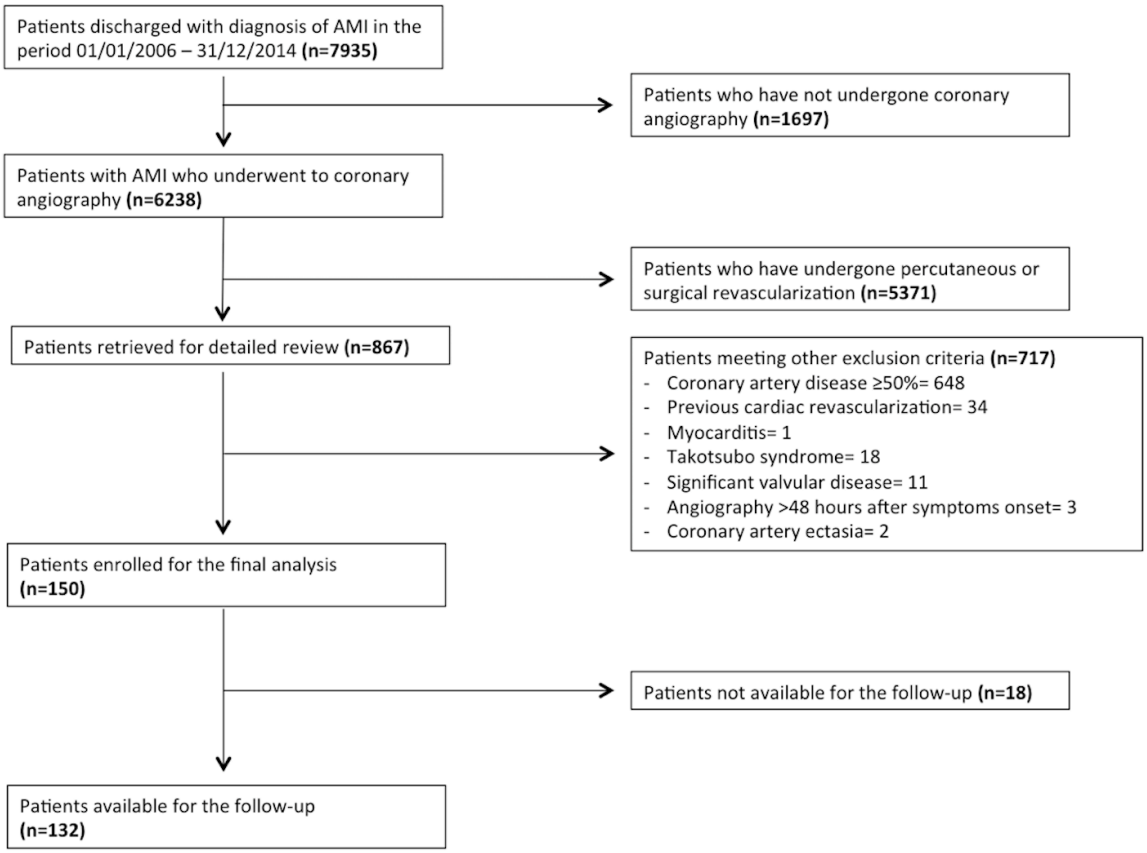


Figure 2. MACE distribution.

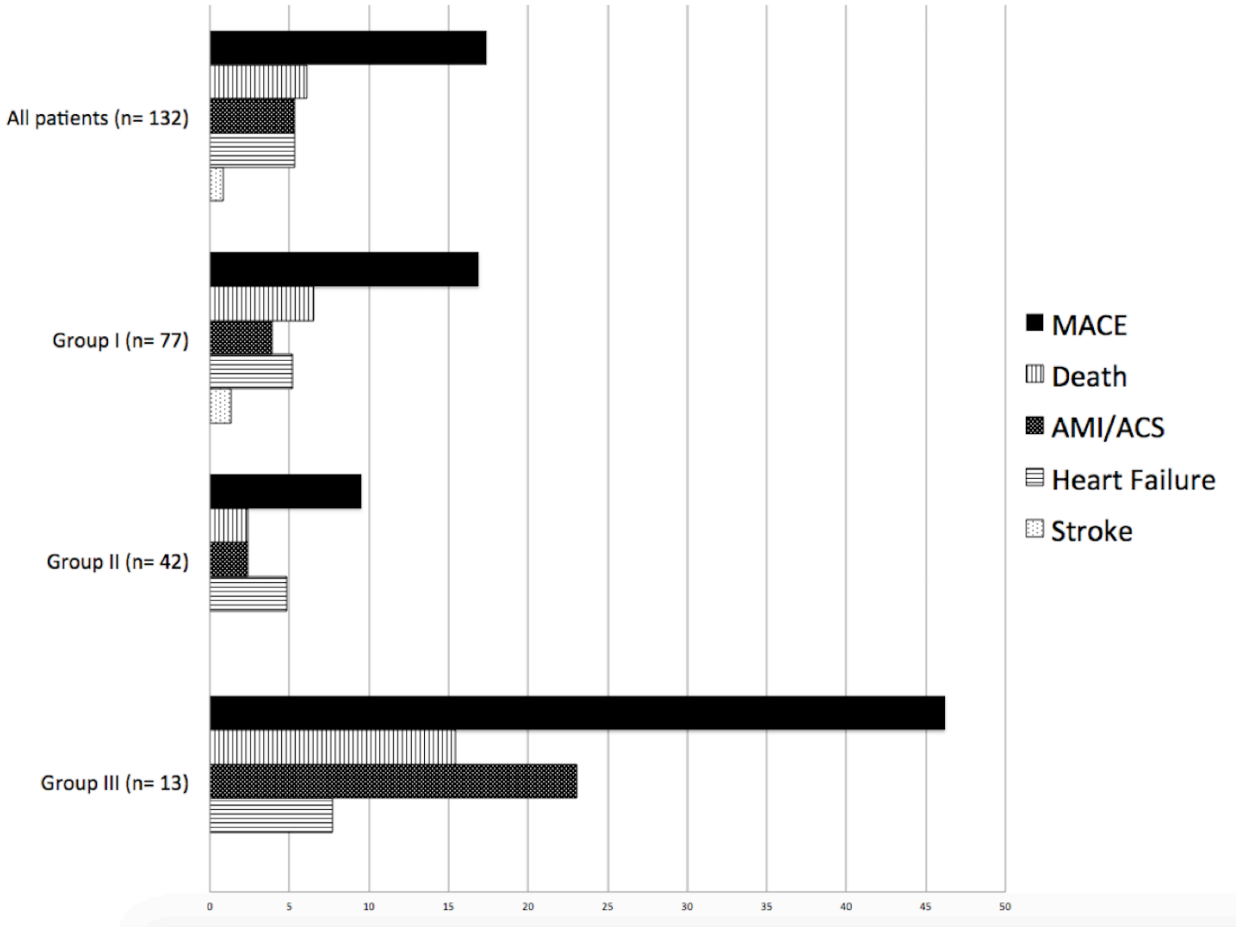
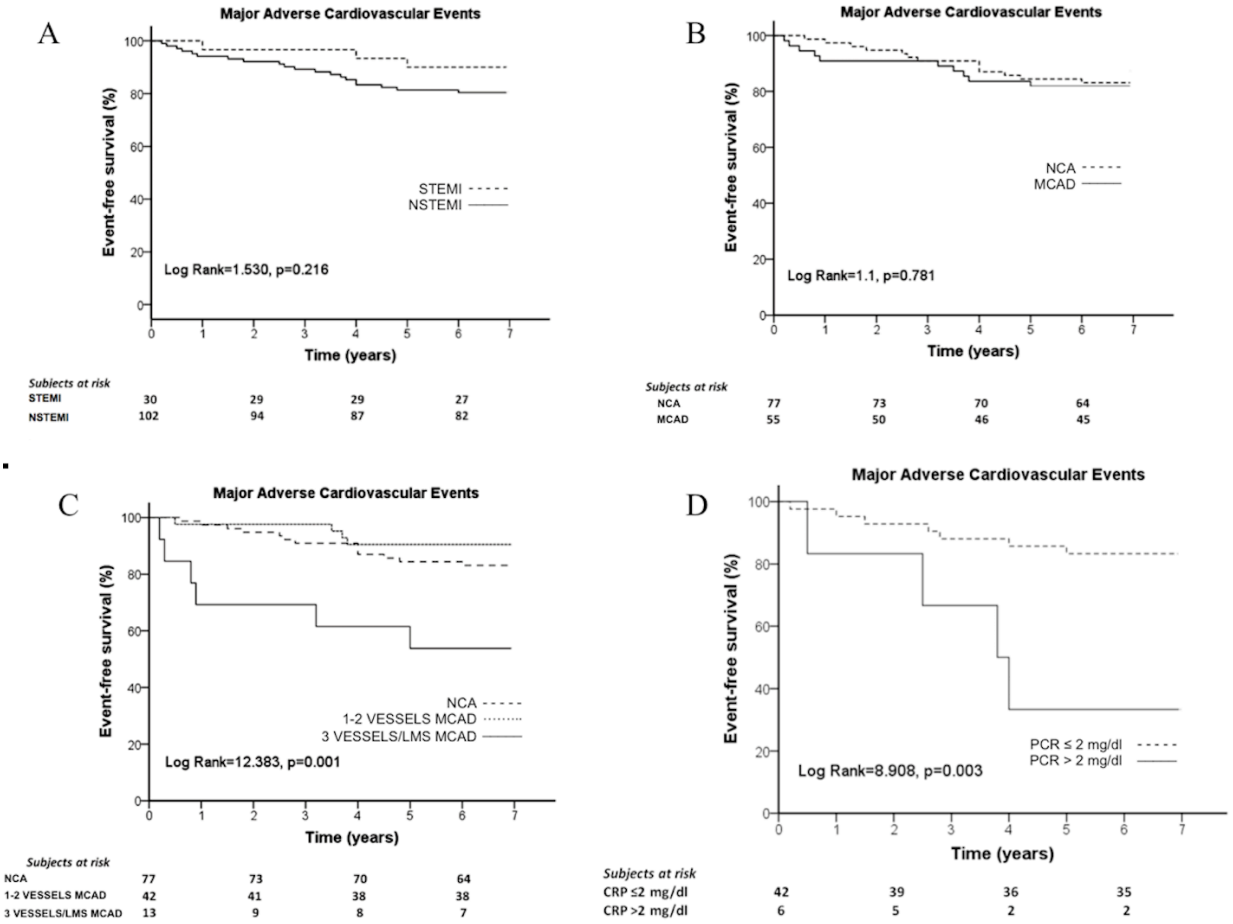


Figure 3. A, Kaplan–Meier curves for the combined endpoint (MACE) according to STEMI versus NSTEMI presentation. B, Kaplan–Meier curves for the combined endpoint (MACE) according to the presence of <30% stenosis (NCA) versus MCAD (≥30% but <50% stenosis). C, Kaplan–Meier curves for the combined endpoint (MACE) according to the CAD distribution: I) NCA (<30% stenosis); II) 1-2 vessels MCAD; III) 3 vessels/LMS MCAD. D, Kaplan–Meier curves for the combined endpoint (MACE) according to CRP levels > 2 mg/dL versus ≤2 mg/dl.

CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease; NCA, normal coronary arteries.



PART III

MINOCA AND SUDDEN CARDIAC DEATH

1. Aims and Methods

Myocardial infarction with non-obstructed coronary arteries (MINOCA) accounts for 1-10% of all causes of acute myocardial infarction (MI)[1].Moreover, MINOCA may be secondary to various specific aetiologies with implications for prognosis[1].The aim of the study was to report clinical and pathological characteristics in a large cohort of decedents of sudden cardiac death (SCD) attributable to MINOCA at autopsy.

MINOCA was defined as evidence of acute MI and/or acute coronary thrombosis in the artery supplying the infarcted myocardium in absence of epicardial coronary artery stenosis >50%[1,2].

1.1 Data collection

We reviewed a database of 5325 consecutive cases of SCD referred to our specialist cardiac pathology center between 1994 and July 2017.Sudden cardiac death was defined as death from a cardiovascular cause within 12 hours of apparent well-being. Clinical information was obtained from referring coroners who were asked to complete a questionnaire inquiring about the demographic characteristics of the decedent, medical history, family history and circumstances of death.All cases underwent detailed autopsy evaluation of the heart, including histological analysis, by expert cardiac pathologists[4]. A minimum of 10 blocks of tissue were taken for histological analysis.Exclusion criteria included specific cardiac conditions as previously reported[3], including myocarditis and Tako-Tsubo cardiomyopathy, which were ruled-out by clinical records examination[3] and through histology[4] .

1.2 Statistical analysis

Results are expressed as mean ± SD for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's t-test for continuous

variables with correction for unequal variance when necessary and chi-square test or Fisher exact test, as appropriate for categorical variables.

2. Results

We identified 37 (0.7%) cases of MINOCA. The majority of decedents were male (n=23; 62%). Mean age at death was 34±16 years (range 13-96 years), and 6 individuals were <18 years of age (table 1). Cardiac symptoms were reported in 18 cases (49%): chest pain (n=12; 32%), dyspnoea (n =6; 16%), syncope (n=2; 5%) and palpitations (n=1; 3%). None of decedents had a pre-mortem diagnosis of ischemic cardiac disease. Death occurred at rest or during daily activities in 36 (97%) individuals, including 9 (24%) who died during sleep. Drug use history was reported in 10 (27%) including marijuana in 3 (8%), cocaine in 2 (5%), heroin in 2 (5%), methadone in 2 (5%), anabolic steroids in 2 (5%), amphetamine in 1 (3%).Of the 10 cases, toxicology testing showed the presence of the same substance in 30% at non toxic levels. The MI age was 24-48 hours in 28 cases (76%) and 1-6 weeks in the rest of decedents. The MI involved the left ventricle (LV) anteroseptal wall in 14 (38%) individuals, LV and right ventricle (RV) subendocardial wall in 9, LV posterobasal in 6, RV and LV diffusely in 5, LV lateral in 2, right atrium in 1. In a minority (n=9; 24%) LV fibrosis was detected in 9(24%), involving a myocardial territory that was different from the one of the MI, with an ischemic (subendocardial/transmural) distribution in 4 (11%).

3. Discussion

Our study reports on the largest autopsy cohorts of individuals with SCD due to MINOCA in which the post-mortem was performed by an expert cardiac pathologist following a standardized protocol.

Most deaths occurred at rest, although almost half of the decedents reported cardiac symptoms. Toxicology analysis was positive in one out of three victims with background of drug use, thus representing a possible aetiological mechanism for both MINOCA and SCD. Ischaemic damage had a diffuse or regional pattern with anteroseptal wall predominating. In addition, replacement fibrosis with an ischemic pattern was identified in a territory that was different from the one involved in the acute MI implying that subclinical MI may have occurred before SCD in this population and may represent a substrate for arrhythmias..

3.1 Limitations of the Study

Our study has some limitations. It is possible that we may have underestimated the proportion of individuals with MINOCA who presented with SCD as the first manifestation because local pathologists may not have referred to our expert center decedents with an established pre-mortem diagnosis of MI.However, our center usually receives a high volume of referrals from SCD (>500 per year), in mostly young decedents and as MI with normal coronary arteries are often referred as uncertain findings we expect that most of these cases were sent for assessment to our center.The lack of ECG in decedents of SCD is also a limitation.

4. Conclusions

In conclusion, MINOCA is an uncommon cause of SCD which usually occurs in young individuals, often at rest or during daily activities and cardiac symptoms are reported in almost half of the cases.The high proportion of decedents reporting use of drugs and anabolic steroids underscores the possible mechanistic link with MINOCA and SCD especially in young individuals.

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6. Tables

Table 1. Overall population characteristics.

Baseline characteristics	**Overall population (n= 37)**
Age (years)	34±16
Males n (%)	23 (62)
Cardiac symptoms n (%)	18 (49)
Drug use n (%)	10 (27)
Death during exercise/ES n (%)	1 (3)
Heart weight (grams)	410±118
LV fibrosis n (%)	9 (24)
MI age 24-48 hours n (%)	28 (76)
Antero-septal MI n (%)	14 (38)

Abbreviations: ES: emotional stress; LV: left ventricular; MI: myocardial infarction.

PART IV

MINOCA AND PHARMACOLOGICAL THERAPY

1. Aims and Methods

MINOCA appears to be not a single entity but a heterogeneous group of different clinical conditions [1-7], thus evidence on the appropriate pharmacological therapy for these patients is scarce, and existing data showed often conflicting results [8,9].

Therefore, we sought to analyse the effect on long-term prognosis of MINOCA patients yielded by treatment with the following pharmacological therapies: acetylsalicylic acid (ASA), dual antiplatelet therapy (DAPT), beta-blockers, statins, renin-angiotensin system (RAS) blockers (angiotensin converting enzyme inhibitors [ACEIs]; angiotensin receptor blockers [ARBs]).

1.1 Patients recruitment

From the 1st March 2012 to 31st March 2018 we enrolled consecutive patients discharged with the diagnosis of AMI fulfilling the criteria stated by the IV Universal definition of AMI [3] with coronary stenosis of <50% in diameter at coronary angiography, discharged from the following Hub Hospitals: Ancona, "Ospedali Riuniti" , Biella, Catanzaro "Pugliese", Chieti, Novara, Roma "Umberto I", Perugia, Trento, Trieste.

Inclusion criteria were: (I) diagnosis of AMI; (II) coronary angiography within 48 hours from onset of symptoms; (III) absence of ≥50% coronary stenosis.

Exclusion criteria were: coronary angiography not performed; previous coronary revascularization; previous cardiac surgery; cardiomyopathy; myocarditis; Takotsubo syndrome; type II MI due to noncoronary mechanisms [4]; coronary ectasia; spontaneous coronary artery dissection (SCAD); significant valvular pathology (at least moderate degree).

Follow-up was carried out as regular outpatient visits and/or by telephone contact.

The study was approved by the local ethics committee and managed in accordance with Good Clinical Practice and the Declaration of Helsinki [10].

1.2 Data collection

The following clinical variables were collected and assessed: a) medical history, risk factors for CAD i.e. hypertension, diabetes mellitus, hyperlipidaemia, smoking and family history of CAD, history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease b) ECG, left ventricular ejection fraction (LVEF) at admission; d) main chemistry parameters at admission.

Pharmacological therapy information was collected from discharge medical report.

1.3 Statistical methods

Continuous variables are expressed as mean (±SD) and categorical variables as percentages. We used chi-square tests and one-way ANOVA for statistical comparisons of clinical characteristics among groups. For the purpose of this study, the primary endpoint (PE) was represented by a composite of the following adverse cardiovascular events: death, AMI or acute coronary syndrome (ACS), heart failure leading to hospitalization (HF), and stroke.

Patients were grouped according to the occurrence of PE. Univariate analyses by Cox proportional hazards models were performed to assess the association clinical variables and pharmacological treatment and outcome. A multivariable Cox regression analysis was performed to evaluate the impact of drugs at discharge on the PE after correction for baseline differences (variables associated with the considered outcome with a P-value <0.10 at baseline).

A forward-conditional Cox proportional model was applied to evaluate the independent predictor of the primary endpoint in the study cohort. Kaplan–Meier method was used to estimate survival probabilities for the combined endpoint. Differences between survival curves were analysed using the log-rank test. A P-value <0.05 was considered significant. Statistical analyses were performed using SPSS package version 23.0 (Chicago, IL, USA).

2. Results

2.1 Baseline characteristics

In our multicentre registry we included n=735 consecutive patients with MINOCA. Among them, follow-up was available in n=621 (84%). Baseline characteristics are reported in Table 1 and therapy at discharge in Table 2.

Patients experiencing an event were more often males (p=0.04), aged ≥75 years (p=0.05), diabetic (p=0.017) and with a history of atrial fibrillation (p=0.036), hypertension (p=0.013), reduced ejection fraction (p=0.049) and with ST-segment elevation presentation (p<0.001) (Table 1).

2.2 Follow-up

At a median follow-up of 90 [IQR:45.6-135] months the composite endpoint occurred in 106 patients (17.1%), among them mortality occurred in 27 patients (4.3%). Kaplan Meier estimates for the primary endpoint are depicted in Figure 1.

The impact of commonly indicated pharmacological agents on the primary endpoint are shown in Table 2.

As shown, less frequent occurrence of the primary endpoint was observed with beta-blockers (60.4% vs 71.3%, HR [95% CI]=0.62[0.41-0.92], p=0.02), whilst a trend for increased risk of events was observed for ASA (93.4% vs 86.8%, HR [95% CI]=2.09 [0.97-4.49], p=0.06). Our results were confirmed at multivariate analysis, after correction for baseline confounders, for beta-blockers (adjusted HR[95%CI]=0.49 [0.31-0.79], p=0.02) and for the increased risk of PE for ASA (adjusted HR[95%CI]=2.47[1.05-5.78], p=0.04) (Table 3, Figure 2A and B, respectively).

In fact, in a multivariate conditional model, the independent predictors of PE were ASA (HR [95% CI]=2.56[1.11-5.97], p=0.04), AF history (HR [95% CI]=1.97 [1.17-3.32], p=0.01), ST-elevation at admission (HR [95% CI]=2.28 [1.45-3.57], p<0.001) and reduced LVEF at admission

(HR [95% CI]=2.26 [1.06-2.63], p=0.02), whereas an inverse association was documented for beta-blockers (HR [95% CI]=0.54[0.33-0.85], p=0.008).

Comparable results were documented at subgroup analysis, in major higher risk subsets of patients (female gender, advanced age, diabetes mellitus, CMR-confirmed MINOCA and reduced LVEF) with no significant interaction for both ASA and beta-blockers (Figure 3).

3. Discussion

The present study showed that among patients with MINOCA the use of beta-blockers was associated with less frequent occurrence of adverse cardiovascular events, whereas ASA was associated with an increased occurrence of adverse events at follow-up.

Other secondary prevention therapies as DAPT, statins, RAS blockers, CCBs, nitrates showed a neutral effect o outcome, according to our results.

There are few contemporary studies analysing the prognostic role of therapy among MINOCA patients [7-9].

A recent Swedish study among 9466 MINOCA patients demonstrated a significant improvement on outcome yielded by statins (HR 0.77, 95% CI 0.68–0.87) and ACE inhibitors/ARB (HR 0.82, 95% CI 0.73–0.93), whereas the use of beta-blockers yielded solely a trend toward beneficial effect on prognosis (HR 0.86, 95% CI 0.74–1.01) [7]. In the same analysis DAPT had a neutral effect on outcome (HR 0.90, 95% CI 0.74–1.08), although this population was highly heterogeneous, thus probably including many cases of myocarditis and Takotsubo syndrome [7,11].

In another study on 396 korean MINOCA patients non-use of RAS blockers and non-use of statins was associated with a significantly increased risk of all-cause mortality (HR, 2.63; 95% CI, 1.08– 6.25; P= 0.033 for RAS blockers and HR, 2.17; 95% CI, 1.04– 4.54; P= 0.039 for statins non-use) [9].

On the other hand, beta-blockers were recently found to be correlated with a higher all-cause mortality risk at meta-regression analysis performed among 36932 patients from n=44 studies [8].

The use of beta-blockers could portend some beneficial cardiovascular effects as reduction in oxygen demand and coronary shear stress by reducing myocardial contractility, heart rate, and blood pressure [6].

The main issue with contemporary available studies reporting on therapy for MINOCA is that data are still biased by large heterogeneity in defining MINOCA [7-9] and often patients with normal troponin or CK-MB were also included [8].

In our study the population sample was derived from detailed analysis of clinical report, and potentially confounding condition as type II MI due to non-coronary causes, myocarditis and Tako-tsubo were a-priori excluded.

Interestingly, our data showed a poor outcome for patients who were prescribed ASA at discharge. One of the possible reasons of the negative impact on prognosis of aspirin, is that non-cardiovascular death accounts for over 90% of deaths observed among MINOCA patients, as recently shown by Williams et al. [12].

Moreover recent trials fails to demonstrated an absolute prognostic benefit of ASA among high-risk patients [13] and healthy elderly patients [14], thus we could speculate that ASA could not be useful (or even harmful) in the absence of obstructive vascular or coronary obstruction.

Although ASA seems to worsen outcome among MINOCA patients, DAPT did not affect long-term prognosis according to our findings.

In addiction, although statins were shown to have long term beneficial effect among over 9000 MINOCA patients (13), this point was not confirmed by our analysis, probably due to more strict inclusion and exclusion criteria adopted in our study.

In a similar manner, RAS blockers proved effective in improving prognosis in patients with MINOCA in two observational studies [7,9], whereas a neutral effect was observed in a recent meta-analysis [8] and in the present study.

With regards to other drugs with vasodilator properties, it has recently been demonstrated that provoked coronary spasm is found in 46.2% of patients with MINOCA [15] with few o none peri-procedural complications [16] and the use of CCBs is recommended in this context [17], not only because of their effectiveness in symptoms control, but also because they are positively related to long-term prognosis [18]. However, in our population CCBs use were not associated with a better outcome, probably because prognosis of this subgroup of MINOCA patients remains poor even in presence of a appropriate vasodilator therapy [16,19], thus questioning the significance of pathological response in coronary vasomotion as a pathogenetic trait or just a marker of increased cardiovascular risk [19].

Taken together, our results may provide practical application, as standard therapy for secondary prevention after MI occurrence, could not be beneficial in the absence of coronary obstruction and/or stenosis ≥ 50%, or even detrimental in some subgroups.

Moreover our findings could raise some question on the physiopathological basis of "true" MINOCA, in which the role of hemorheology and/or haemodynamic aspects can be more important than classical atherosclerotic factors (i.e. plaque disruption) [20] in favouring ischemic myocardial injury, thus supporting the benefit associated with beta-blockers therapy rather than anti-platelet drugs.

Since high-quality data from prospective, randomized controlled studies are still lacking, further insights will be certainly provided from a multicentre ongoing trial aimed to determine whether beta-blockade compared to no oral beta-blockade, and whether ACEI/ARB compared to no ACEI/ARB, reduce the composite endpoint of death of any cause and readmission because of AMI, ischemic stroke or heart failure in patients discharged with MINOCA and with no clinical signs of heart failure and with left ventricular (LV) systolic ejection fraction ≥40% (ClinicalTrials.gov Identifier: NCT03686696).

3.1 Limitations of the study

We enrolled only MINOCA patients who underwent coronary angiography but angiographic results were not adjudicated by a core laboratory.

We excluded patients with myocarditis, Takotsubo syndrome and type II MI secondary to noncoronary causes, thus our population could be substantially different from other contemporary studies in which inclusion criteria are more inclusive.

We do not report data on CMR, endomyocardial biopsy or provocative testing to rule out coronary spasm as these tests were not part of a systematic assessment protocol and such information was available in a small number of patients in our database (CMR in 21%). However, in our study, patients with CMR-confirmed MINOCA showed a similar behaviour compared with those who could not undergo CMR.

We do not report on a matched obstructive CAD control group for comparison as it was our aim to assess the prognostic impact of therapy among MINOCA patients.

4. Conclusions

In this multicentre registry the use of beta-blockers significantly reduced the risk of mortality and major cardiovascular events among patients with myocardial infarction and non-obstructed coronary arteries (MINOCA), whereas antiplatelet drugs, in single or dual therapy did not demonstrate any benefit, displaying even a potential harmful impact on the outcomes, especially in certain subsets of patients. Therefore, patients with MINOCA represent a heterogeneous category of acute coronary syndrome patients, where an adequate diagnostic assessment and risk stratification can condition the treatment and the outcome. Future largest studies will certainly provide a better comprehension of the pathophysiological mechanisms and a definition of the prognostic tools for optimizing the management of these patients. Prospective studies are necessary to test the hypotheses generated by our findings.

5. References

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6. Tables and figures

Table 1.

	Total, n=621	PE, n=106	No PE, n=515	P value
Demographics				
Age (±SD)	65.1±13.9	67.3±14.5	64.6±13.8	0.07
Female (%)	55.4	47.2	57.1	0.07
Medical history, %				
Hypertension	61.4	72.5	59	0.01
Diabetes mellitus	16.1	24.5	14.3	0.02
Hyperlipidaemia	45.1	39.4	46.3	0.22
Smoking	30.7	32.5	30.4	0.57
CAD family history	28.5	20.8	30.1	0.001
AF history	12.5	19.8	11.1	0.04
COPD	4.5	9.3	3.7	0.06
Cerebrovascular disease	5.1	9.3	4.4	0.08
Prior AMI (%)	5.6	6.8	5.4	0.59
ECG at admission, %				
ST-elevation	17.7	34.9	14.2	<0.001
LVEF <50% (admission), %	25.1	33.0	23.5	0.049
CMR-confirmed MINOCA, %	21.6	26.4	20.6	0.19
Acute complications, %	4.2	1.1	3.1	0.39
Blood testings				
Creatinine (mg/dl)	1.09±0.5	1.0±0.0	1.1±0.6	0.68
Haemoglobin (g/dl)	13.2±1.6	12.9±1.6	13.6±1.6	0.53

Baseline characteristics and univariate analysis for the primary endpoint (PE).

AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LMS, left main stem; LVEF, left ventricular ejection fraction; MCAD, mild coronary artery disease; NCA, normal coronary arteries; PE, primary end-pont.

Table 2.

	Total, n= 621	PE, n=106	No PE, n=515	P value
Aspirin (%)	87.9	93.4	86.8	0.07
DAPT (%)	58.8	60.0	58.5	0.82
P2Y12-I (%)	60.3	57.4	60.9	0.56
Beta-blockers (%)	69.4	60.4	71.3	0.03
ACE-I (%)	57.1	58.5	56.8	0.83
ARB (%)	14.5	19.5	13.7	0.11
Statins (%)	81.0	80.2	81.2	0.79
CCBs (%)	22.7	26.8	21.9	0.32
Nitrates (%)	18.6	19.3	18.4	0.88

Pharmacological therapy and univariate analysis for the primary endpoint (PE).

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CCB, calcium-channel blockers; DAPT, dual anti-platelet therapy; PE, primary end-point; P2Y12-I, P2Y12-inhibitors.

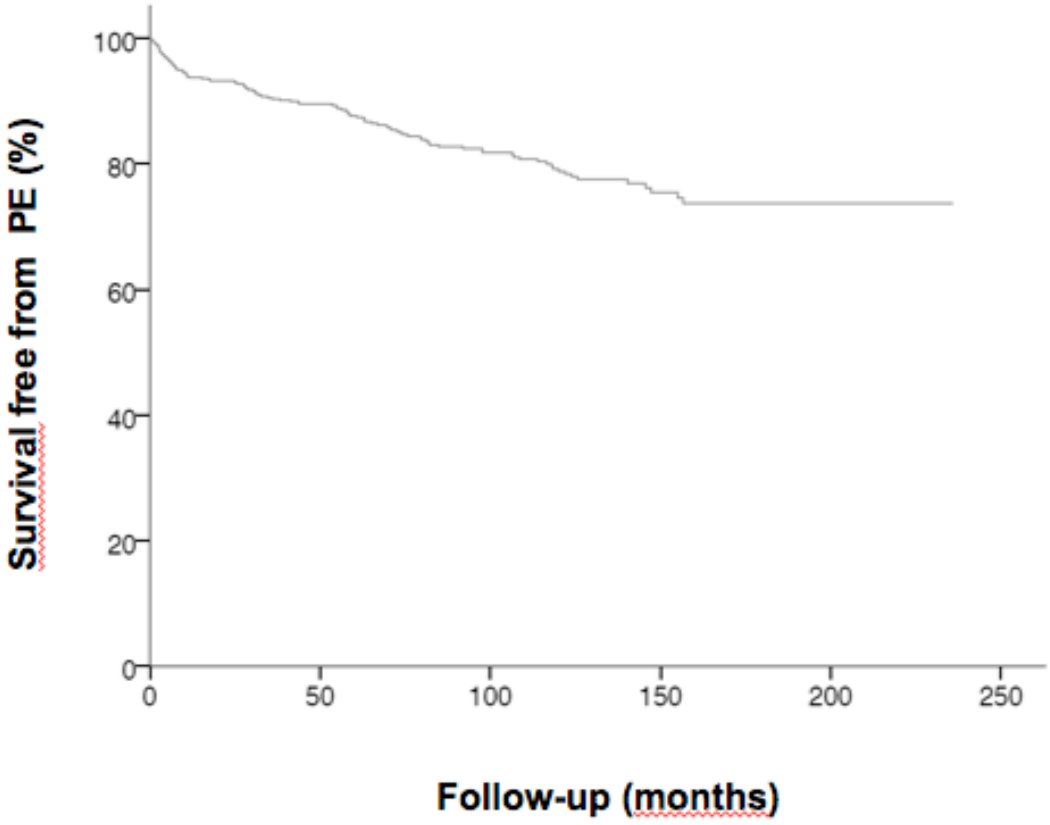
Table 3.

	Primary endpoint		Unadjusted HR	unadjusted	Adjusted HR	adjusted
	PE	**No PE**	(95% CI)	P value	(95% CI)	P value
ACEI/ARB (n=430)	78 (73.6)	352 (68.3)	1.29 (0.83-1.99)	0.26	0.70 (0.40-2.21)	0.21
Statins (n=503)	85 (80.2)	418 (81.2)	1.05 (0.65-1.69)	0.86	1.67 (0.91-3.05)	0.10
DAPT (n=325)	54 (60)	271 (58.5)	1.04 (0.68-1.59)	0.86	2.25 (0.58-8.79)	0.24
ASA (n=546)	99 (93.4)	447 (86.8)	2.09 (0.97-4.49)	0.06	2.47 (1.05-5.78)	0.04
P2Y12-I (n=339)	54(57.4)	285 (60.9)	0.84 (0.56-1.27)	0.41	0.45 (0.22-1.68)	0.24
CCB (n=123)	22 (26.8)	101 (21.9)	1.14 (0.69-1.88)	0.61	1.41 (0.77-2.50)	0.27
B-blockers (n=402)	61 (60.4)	341 (71.3)	0.62 (0.41-0.92)	0.02	0.49 (0.31-0.79)	0.02

Multivariate Cox model analysis for the primary endpoint according to commonly indicated pharmacological agents.

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CCB, calcium-channel blockers; DAPT, dual anti-platelet therapy; PE, primary end-point; P2Y12-I, P2Y12-inhibitors.

Figure 1


Survival free from PE (%)
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80
60
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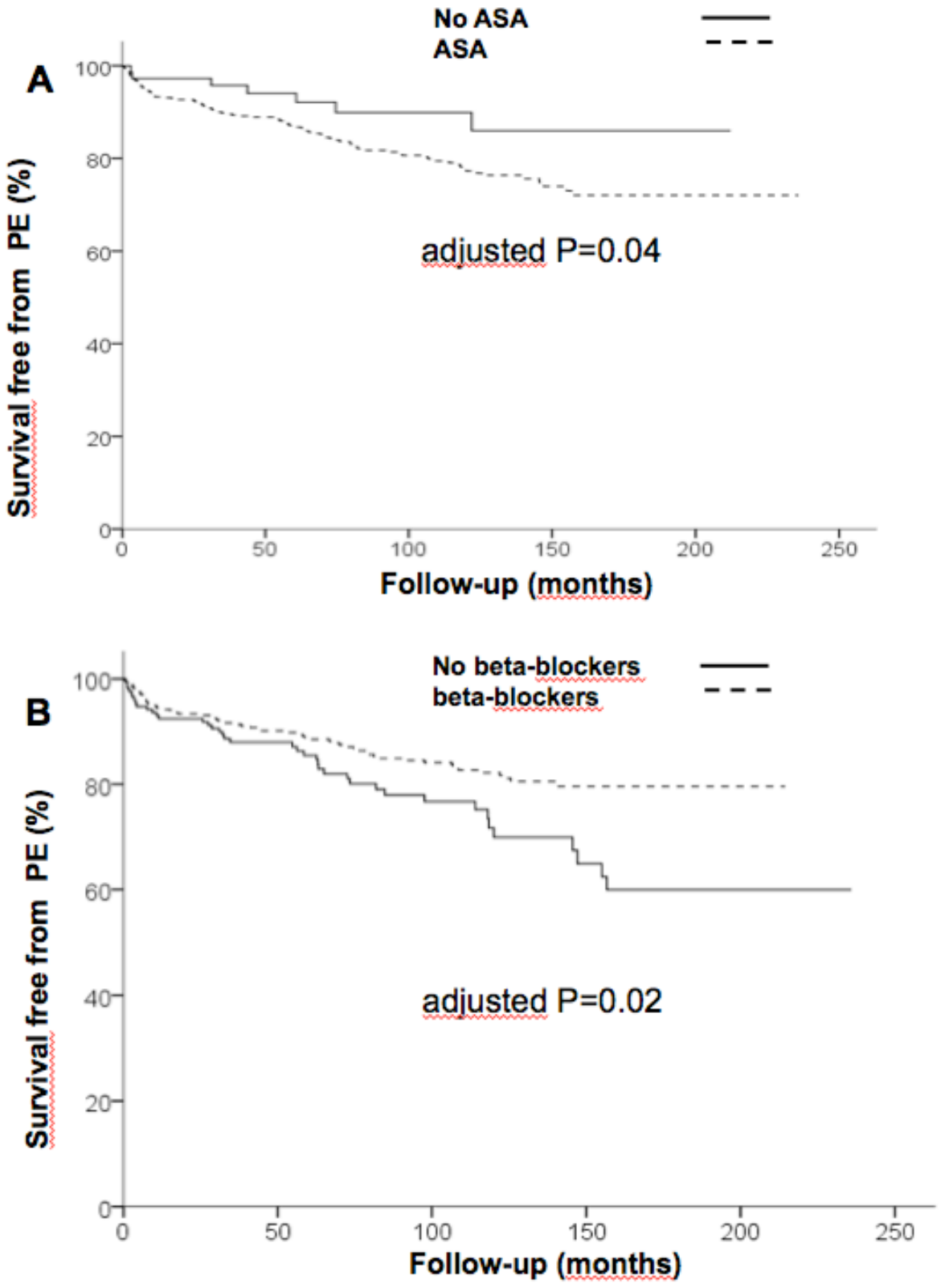
0
50
100
150
200
250
Follow-up (months)

Figure 2


A
No ASA
ASA
Survival free from PE (%)
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250
Follow-up (months)
adjusted P=0.04
B
No beta-blockers
beta-blockers
Survival free from PE (%)
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Follow-up (months)
adjusted P=0.02

Figure 3

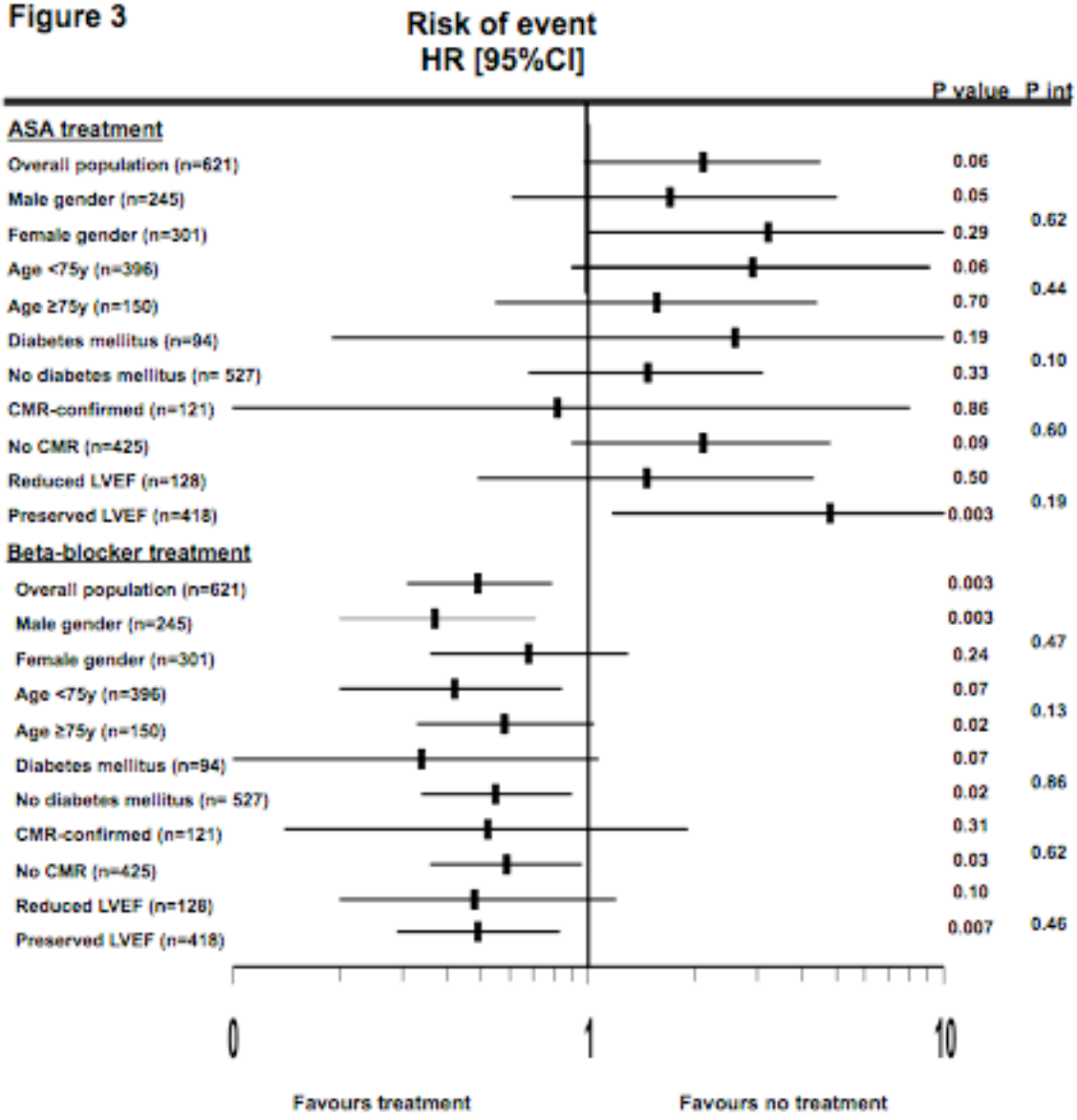
Risk of event
HR [95%CI]
P value
P int
ASA treatment
Overall population (n=621)
Male gender (n=245)
Female gender (n=301)
Age <75y (n=396)
Age ≥75y (n=150)
Diabetes mellitus (n=94)
No diabetes mellitus (n= 527)
CMR-confirmed (n=121)
No CMR (n=425)
Reduced LVEF (n=128)
Preserved LVEF (n=418)
0.06
0.05
0.62
0.29
0.06
0.44
0.70
0.19
0.10
0.33
0.86
0.60
0.09
0.50
0.19
0.003
Beta-blocker treatment
Overall population (n=621)
Male gender (n=245)
Female gender (n=301)
Age <75y (n=396)
Age ≥75y (n=150)
Diabetes mellitus (n=94)
No diabetes mellitus (n= 527)
CMR-confirmed (n=121)
No CMR (n=425)
Reduced LVEF (n=128)
Preserved LVEF (n=418)
0.003
0.003
0.47
0.24
0.07
0.13
0.02
0.07
0.86
0.02
0.31
0.62
0.03
0.10
0.46
0.007
0
1
10
Favours treatment
Favours no treatment

Figure legend

Figure 1

Kaplan–Meier curve for the combined primary endpoint (PE) in the overall study population.

Figure 2

2A, Kaplan–Meier curves for the combined primary endpoint (PE) according to the prescription of acetylsalicylic acid (ASA) at discharge versus no prescription.

2B, Kaplan–Meier curves for the combined primary endpoint (PE) according to the according to the prescription of beta-blockers at discharge versus no prescription.

Figure 3

Forrest plot analysis for the risk of the the combined primary endpoint (PE) in major higher risk subsets of patients according to the use of ASA and beta-blocker.