



## MINOCA: The caveat of absence of coronary obstruction in myocardial infarction



Nousjka P.A. Vranken<sup>a,1,2</sup>, Tobias F.S. Pustjens<sup>b,\*,1,2</sup>, Evelien Kolkman<sup>c,2</sup>, Renicus S. Hermanides<sup>d,2</sup>, Sebastiaan C.A.M. Bekkers<sup>a,e,2</sup>, Martijn W. Smulders<sup>a,e,2</sup>, Yvonne J.M. van Cauteren<sup>a,e,2</sup>, Jordi Heijman<sup>a,e,2</sup>, Saman Rasoul<sup>a,b,2</sup>, Jan P. Ottervanger<sup>d,2</sup>, Arnoud W.J. van 't Hof<sup>a,b,d,2</sup>

<sup>a</sup> Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands

<sup>b</sup> Department of Cardiology, Zuyderland Medical Centre, Heerlen, the Netherlands

<sup>c</sup> Diagram Diagnostic Research and Management, Zwolle, the Netherlands

<sup>d</sup> Department of Cardiology, Isala Hospital, Zwolle, the Netherlands

<sup>e</sup> Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands

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### ABSTRACT

**Aims:** Whether patients with MINOCA (myocardial infarction with non-obstructive coronary arteries) have better outcomes than patients with obstructive coronary artery disease remains contradictory. The current study focussed on the clinical profile and prognosis of MINOCA patients.

**Methods and results:** We performed a retrospective analysis of patients with acute coronary syndrome (ACS) admitted to the Isala hospital in Zwolle, the Netherlands, between 2006 and 2014. A total of 7693 patients were categorized into three groups: MINOCA, single-vessel obstructive ACS (SV-ACS), and multi-vessel obstructive ACS (MV-ACS). MINOCA patients (5.2% of the total population) were more likely to be female (51.5% vs. 30.3% and 26.0% in SV-ACS and MV-ACS, respectively,  $p < 0.001$  for both). The prevalence of risk factors in the MINOCA group was in between the SV-ACS and MV-ACS groups. Logistic regression revealed a lower odds of dying in SV-ACS (odds ratio (OR) = 0.70 ( $p = 0.04$ )) and a similar odds in MV-ACS (OR = 0.88,  $p = 0.45$ ) compared to MINOCA.

**Conclusions:** Patients with MINOCA show an 'intermediate' risk profile with mortality rates in between those of both ACS groups. Hence, MINOCA should be recognised as a potential risk factor for mortality, requiring adequate treatment and follow-up.

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### 1. Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) occurs frequently in patients with acute coronary syndrome (ACS) and represents a conundrum with multiple underlying aetiologies [1–4]. The prevalence of MINOCA varies from 1 to 15%, depending on the population examined and the definition used [5,6]. The MINOCA population shows a predilection for younger, female patients and is more prevalent in non-ST-elevation ACS (NSTE-ACS) [1,5,7,8]. Although this syndrome has

gained increasing attention, it remains a diagnostic and therapeutic challenge for physicians [4].

To diagnose MINOCA it requires (1) an acute myocardial infarction (AMI), (2) demonstration of non-obstructive coronary arteries by invasive coronary angiography defined as stenosis  $< 50\%$  in any potential infarct-related epicardial artery, and (3) no clinically overt alternative explanation [2]. Position papers from the European Society of Cardiology and American Heart Association recommend that MINOCA should be considered as a working diagnosis requiring further diagnostic workup [2,3].

Although several studies suggest that MINOCA patients may have better clinical outcome than myocardial infarction with obstructive coronary artery disease (MICAD), others suggest that MINOCA should not be considered a benign condition [1,9–13] showing comparable outcome between MINOCA and MICAD patients [8,14]. This might be due to the fact that outcomes in MINOCA are generally compared with a 'general MICAD group', without taking single and multi-vessel disease into account [1]. The

\* Corresponding author at: Department of Cardiology, Zuyderland Medical Centre, P.O. Box 5500, NL-6130 MB Sittard-Geleen, the Netherlands.

E-mail address: [t.pustjens@gmail.com](mailto:t.pustjens@gmail.com) (T.F.S. Pustjens).

<sup>1</sup> Authors contributed equally.

<sup>2</sup> This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

presence of multi-vessel disease obviously predisposes the patient to a vastly increased risk of future cardiac events. Hence, comparisons between MINOCA and a general MICAD group should be interpreted with caution. Therefore, the current study aimed to provide insight in the patient profile and prognosis of MINOCA compared to ACS with either single or multi-vessel disease.

## 2. Methods

### 2.1. Study population

We performed a retrospective analysis of patients with ACS admitted and treated at the Isala hospital in Zwolle, the Netherlands. All adult patients with suspected type 1 ACS admitted between January 2006 and December 2014 were registered. The applied definitions for ACS were consistent with current guidelines [15]. Informed consent was obtained from all patients. Data on baseline characteristics, cardiovascular risk factors, complications, discharge medication, and clinical outcomes were prospectively collected. Enzymatic myocardial infarction size was estimated by peak creatine kinase (CK) and CK-MB. The following outcome data were obtained at 30 days and 1 year: all-cause mortality, recurrent revascularisation (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), recurrent AMI, bleeding complications, and cerebrovascular accident. Clinically overt bleeding was defined as a drop in haemoglobin  $\geq 2$  mmol/L or requiring a blood transfusion of  $\geq 2$  red packed cells. The combined endpoint of major adverse cardiac events (MACE) consisted of the composite of all-cause mortality, recurrent unscheduled revascularisation, and recurrent AMI. All-cause mortality at maximum follow-up was obtained by consulting the Dutch municipal personal records database at the last known residence of the patient. Patients presenting with an out-of-hospital cardiac arrest were excluded from analysis. Data regarding medication use were depicted at discharge and follow-up.

### 2.2. Subgroup analysis

To assess differences in patient characteristics and outcomes, patients were categorized into three groups: MINOCA, single vessel obstructive ACS (SV-ACS), defined as  $\geq 50\%$  stenosis in one epicardial coronary artery, and multi-vessel obstructive ACS (MV-ACS), defined as  $\geq 50\%$  stenosis in at least two epicardial coronary arteries or left main coronary artery. Patients with MINOCA were compared with SV-ACS and MV-ACS.

### 2.3. Statistical analysis

Continuous variables are described as mean with standard deviation or median and [interquartile range] when appropriate. The independent samples *T*-test or Mann-Whitney *U* test was used to assess group differences for continuous variables. Categorical data are described as frequency and percentage within groups and the Pearson's  $\chi^2$ -test (or Fisher's exact test in case  $> 20\%$  of cells show an expected count  $< 5$ ) was used to assess group differences. To account for multiple testing, the Bonferroni correction was applied. Two pair-wise comparisons were performed in all univariate univariable analyses, thus all presented *p*-values are Bonferroni corrected values (Tables 1–4, S1). In addition to the univariate analyses, the MINOCA group was compared to a case-control matched SV-ACS and MV-ACS group.

All-cause mortality was analysed using Kaplan-Meier statistics with group comparisons performed by the log-rank test. Using univariate multivariable logistic regression, the grouping variable (MINOCA, SV-ACS, MV-ACS) as well as a set of variables with signif-

icant differences between groups (as revealed by univariate univariable analysis) were incorporated to estimate the contributions of individual parameters on mortality. Results were given as odds ratios (OR) with corresponding 95% confidence interval (CI) and *p*-value.

A two-sided  $\alpha < 0.05$  was considered statistically significant. All statistical analyses were performed in IBM SPSS version 26.0 (IBM Corp, New York, NY, USA).

## 3. Results

A total of 9198 adult patients presenting with ACS were enrolled in the registry. Few patients showed missing data in the majority of demographical and clinical parameters ( $n = 227$ ) and were therefore excluded. Fourteen patients showed conflicting results in parameters concerning coronary angiography and were excluded. In some patients, data concerning coronary artery disease status was lacking ( $n = 914$ , of which  $n = 587$  did not undergo coronary angiography and a conservative treatment was indicated, in  $n = 93$  data on the angiography results were missing, and in  $n = 234$  patients it was unknown whether coronary angiography was performed or not, while data on the results of a potential angiography was missing as well). Remaining out-of-hospital cardiac arrest patients ( $n = 350$ ) were excluded. A total of 7693 cases remained eligible for analysis.

The prevalence of MINOCA was 5.2%, while SV-ACS and MV-ACS were diagnosed in 42.5% and 52.3%, respectively. The proportion of ST-elevation ACS (STE-ACS) was smaller in the MINOCA group compared to both SV-ACS and MV-ACS: 41.5% vs. 72.4% ( $p < 0.001$ ) and 60.8% ( $p < 0.001$ ), respectively. MINOCA patients were more likely to be female (51.5% vs. 30.3% and 26.0%, respectively, both comparisons  $p < 0.001$ ), with a median age (64 [53–74] years) comparable to SV-ACS patients (62 [52–72] years,  $p = 0.30$ ), but younger than MV-ACS patients (68 [59–77] years,  $p < 0.001$ ). The prevalence of risk factors including hypertension, hypercholesterolemia, and diabetes mellitus in the MINOCA group was intermediate between those of both ACS groups (Table 1).

Peak CK levels and CK-MB were lowest in patients with MINOCA as compared to SV-ACS and MV-ACS patients, whereas troponin levels were significantly higher in SV-ACS similar as compared to MV-ACS. Creatinine levels were comparable in MINOCA and SV-ACS, and higher in MV-ACS compared to MINOCA patients (Table 2).

Group differences in medication use at discharge and 30 days and 1 year following admission are provided in Table 3. Besides coumarin derivatives, MINOCA patients used less oral antiplatelet therapy compared to both MICAD groups (Table 3). Similar results were found when patients who underwent CABG within one year following index hospitalisation were excluded from analysis ( $n = 1104$ ) (Supplementary material, Table S1).

### 3.1. Clinical outcome

Data with regards to survival status were available in 7511 (97.6%) patients. A small fraction of patients ( $n = 46$ , 0.6%) died within approximately 24 h of hospital admission (in the MINOCA group:  $n = 0$ , in SV-ACS  $n = 10$ , and in MV-ACS:  $n = 36$ ). Consequently, a total of 7465 patients (97.0%) remained eligible for survival analysis (Fig. 1). The median follow-up duration with regards to survival status was 4.5 [2.4–6.7] years. All-cause mortality at 1 year follow-up in MINOCA and SV-ACS were 3.9% vs. 4.4% ( $p = 1.00$ ) respectively, but was significantly lower in MINOCA as compared to MV-ACS (8.6%,  $p = 0.002$ ; Table 4). At long-term follow-up, mortality rates in MINOCA patients were non-significantly higher than in SV-ACS: 16.3% vs. 12.5% ( $p = 0.07$ ),

**Table 1**  
Patient demographics and cardiovascular risk factors.

	MINOCA (n = 402; 5.2%)	SV-ACS (n = 3266; 42.5%)	MV-ACS (n = 4025; 52.3%)	p-value MINOCA vs SV-ACS	p-value MINOCA vs MV-ACS
Presentation with STE-ACS n(%)	167(41.5)	2365(72.4)	2447(60.8)	<0.001	<0.001
Female gender n(%)	207(51.5)	990(30.3)	1045(26.0)	<0.001	<0.001
Age (y)	64[53–74]	62[52–72]	68[59–77]	0.304	<0.001
BMI (kg/m <sup>2</sup> )	26[24–29]	26[24–29]	27[25–29]	1.00	0.208
Hypertension n (%)	194(48.6)	1193(35.7)	1947(58.2)	<0.001	1.00
Hypercholesterolemia n (%)	90(22.8)	667(20.7)	1190(25.7)	0.670	0.006
Diabetes mellitus n (%)	55(13.8)	308(9.5)	737(18.5)	0.014	0.042
Smoker n (%)	95(23.9)	1340(41.5)	1291(32.6)	<0.001	<0.001
Former smoker n (%)	60(24.0)	431(28.4)	591(25.4)	0.304	1.00
Positive family history n (%)	140(35.2)	1216(37.8)	1381(35.0)	0.624	1.00
Peripheral artery disease n (%)	5(3.2)	28(2.4)	91(6.1)	1.00	0.296
Renal failure n (%)	8(5.2)	18(1.5)	65(4.4)	0.014	1.00
Previous CVA n (%)	11(2.8)	81(2.5)	155(3.9)	1.00	0.524
Previous AMI n (%)	23(5.8)	246(7.6)	627(15.7)	0.372	<0.001
Previous PCI n (%)	32(8.0)	304(9.4)	582(14.6)	0.756	<0.001
Previous CABG n (%)	8(2.0)	55(1.7)	396(9.9)	1.00	<0.001
Previous revascularisation procedure n (%)	37(9.2)	339(10.4)	802(20.0)	0.930	<0.001
PCI in acute phase n (%)	7 (1.8)	2962 (90.7)	3019 (75.1)	<0.001	<0.001
CABG in acute phase n (%)	3 (0.8)	63 (2.0)	853 (22.1)	0.178	<0.001

Numerical variables expressed as median [interquartile range].

AMI: acute myocardial infarction, CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, MINOCA: myocardial infarction with non-obstructive coronary arteries, MV-ACS: multivessel obstructive acute coronary syndrome, STE-ACS: ST-elevation acute coronary syndrome, SV-ACS: single vessel obstructive acute coronary syndrome.

**Table 2**  
Laboratory values.

	MINOCA	SV-ACS	MV-ACS	p-value MINOCA vs SV-ACS	p-value MINOCA vs MV-ACS
CK at admission (U/L)	109[75–183]	144[88–287]	153[90–307]	<0.001	<0.001
Peak CK < 24 h admission (U/L)	127[81–233]	504[172–1540]	401[158–1150]	<0.001	<0.001
CKMB at admission (ng/L)	15[11–23]	18[13–36]	20[14–42]	<0.001	<0.001
CRP at admission (mg/L)	4[2–12]	3.2[1.8–7.2]	4[2–10]	0.060	1.00
Nt-proBNP at admission (pmol/L)	234[99–1475]	180[66–657.3]	358.5[110–1210]	<0.001	1.00
Troponin at admission (ng/L)	280[78–688]	130[60–360]	146[63–420]	0.022	1.00
Creatinine at admission (umol/L)	76[64–90]	77[66–90]	83[70–99]	0.764	<0.001

Numerical variables expressed as median [interquartile range].

CK: creatine kinase, CKMB: creatine kinase myocardial band, CRP: C-reactive protein, NT-proBNP: N-terminal prohormone B-type natriuretic peptide. Other abbreviations as in Table 1.

**Table 3**  
Use of medication at discharge and follow-up.

	MINOCA	SV-ACS	MV-ACS	p-value MINOCA vs SV-ACS	p-value MINOCA vs MV-ACS
DAPT at discharge n (%)	91(25.3)	2708(88.1)	2585(68.7)	<0.001	<0.001
DAPT at 30 days n (%)	63(19.9)	2270(85.3)	1975(64.5)	<0.001	<0.001
DAPT at 1 year n (%)	21(9.3)	1017(53.1)	902(41.0)	<0.001	<0.001
P2Y12 inhibitor at discharge n (%)	105(29.2)	2861(93.1)	2787(74.1)	<0.001	<0.001
P2Y12 inhibitor at 30 days n (%)	75(23.7)	2468(92.7)	2190(71.5)	<0.001	<0.001
P2Y12 inhibitor at 1 year n (%)	24(10.6)	1141(59.6)	1031(46.9)	<0.001	<0.001
Coumarin at discharge n (%)	54(15.0)	243(7.9)	489(13.0)	<0.001	0.546
Coumarin at 30 days n (%)	54(17.0)	308(11.6)	505(16.5)	0.010	1.00
Coumarin at 1 year n (%)	38(16.7)	211(11.0)	355(16.1)	0.022	1.00
ASA at discharge n (%)	222(61.8)	2850(92.7)	3288(87.4)	<0.001	<0.001
ASA at 30 days n (%)	170(53.6)	2395(90.0)	2617(85.4)	<0.001	<0.001
ASA at 1 year n (%)	101(44.5)	1670(87.3)	1790(81.4)	<0.001	<0.001

ASA: acetylsalicylic acid, DAPT: dual antiplatelet therapy. Other abbreviations as in Table 1.

but significantly lower than in MV-ACS (22.1%,  $p = 0.02$ ). These differences translated to significantly different survival rates, in which the MINOCA group survival curve was intermediate between both MICAD groups (Fig. 1).

Multivariable univariate logistic regression analysis revealed no significant contribution of hypertension and hypercholesterolemia to long-term mortality, and a borderline significant contribution of type of ACS (STE-ACS compared to NSTEMI-ACS): OR = 1.15 (95% CI 1.00–1.32,  $p = 0.05$ ). After rebuilding the model while excluding

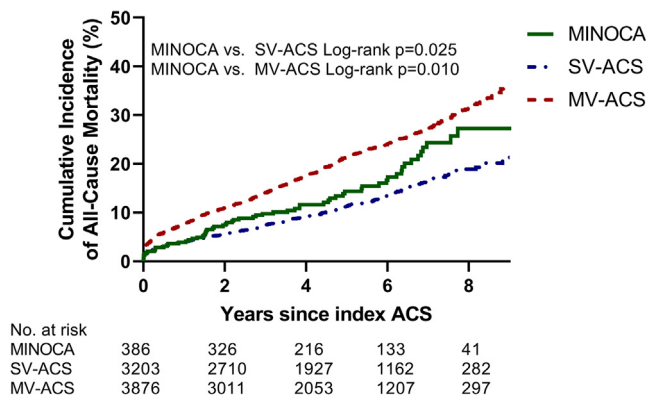
hypertension and hypercholesterolemia, type of ACS showed to have a significant impact on mortality risk: OR = 1.23 (95% CI 1.06–1.42,  $p = 0.01$ ). Advanced age, presentation with STE-ACS, diabetes, current smoking, and higher creatinine levels at admission appeared to be significantly associated with increased odds of dying (Table 5). Moreover, the same model showed a significantly lower odds of dying in SV-ACS patients compared to MINOCA: OR = 0.70 (95% CI 0.50–0.98,  $p = 0.04$ ), while similar odds were found in MV-ACS: OR = 0.88 (95% CI 0.64–1.22,  $p = 0.45$ ) (Table 5).

**Table 4**  
Clinical outcomes.

	MINOCA	SV-ACS	MV-ACS	p-value MINOCA vs SV-ACS	p-value MINOCA vs MV-ACS
PCI* <30 days n (%)	0(0.0)	82(2.8)	240(6.7)	0.002	<0.001
PCI* <1 year n (%)	1(0.4)	173(9.1)	407(16.8)	<0.001	<0.001
CABG* <30 days n (%)	3(0.8)	69(2.4)	903(24.8)	0.122	<0.001
CABG* <1 year n (%)	3(1.3)	91(4.8)	1000(37.0)	0.032	<0.001
Recurrent AMI < 30 days n (%)	0(0.0)	19(0.7)	38(1.1)	0.514	0.090
Recurrent AMI < 1 year n (%)	3(1.3)	36(1.9)	74(3.2)	1.00	0.248
Bleeding < 30 days n (%)	16(4.4)	129(4.4)	836(23.0)	1.00	<0.001
Bleeding < 1 year n (%)	19(8.2)	158(8.3)	925(35.0)	1.00	<0.001
CVA < 30 days n (%)	0(0.0)	11(0.4)	10(0.3)	1.00	1.00
CVA < 1 year n (%)	0(0.0)	20(1.1)	21(0.9)	0.520	0.500
All-cause mortality in hospital n (%)	7(1.8)	51(1.6)	142(3.7)	1.00	0.112
All-cause mortality < 30 days n (%)	7(1.7)	72(2.2)	172(4.3)	1.00	0.028
All-cause mortality < 1 year n (%)	15(3.9)	141(4.4)	336(8.6)	1.00	0.002
All-cause mortality at maximum follow-up n (%)	63(16.3)	403(12.5)	863(22.1)	0.074	0.018
Days between admission-all cause mortality	809[380–1957]	848[153–1718]	659[90–1479]	0.578	0.052
MACE < 30 days n (%)	10(2.8)	218(7.5)	1274(34.9)	0.002	<0.001
MACE < 1 year n (%)	21(9.3)	384(20.0)	1636(57.9)	<0.001	<0.001

Numerical variables expressed as median [interquartile range]. \*PCI and CABG events excluding PCI and CABG in the acute phase (following presentation at the cardiac emergency department).

CABG: coronary artery bypass grafting, MACE: major adverse cardiovascular event, PCI: percutaneous coronary intervention. Other abbreviations as in Table 1.



**Fig. 1.** Cumulative crude all-cause mortality across groups at maximum follow-up. Abbreviations as in Table 1.

**Table 5**  
Multivariable logistic regression analysis to predict all-cause mortality at maximum follow-up.

	OR	95% CI	p-value
Age (y)	1.093	1.085–1.101	<0.001
Current smoking	1.606	1.363–1.894	<0.001
Diabetes mellitus	1.827	1.539–2.169	<0.001
STE-ACS <sup>1</sup>	1.230	1.062–1.424	0.006
Creatinine at admission	1.011	1.009–1.012	<0.001
SV-ACS <sup>2</sup>	0.699	0.499–0.979	0.037
MV-ACS <sup>2</sup>	0.881	0.635–1.222	0.447

1: compared to NSTEMI-ACS.

2: compared to myocardial infarction with non-obstructive coronary arteries.

CI: confidence interval, OR: odds ratio. Other abbreviations as in Table 1.

Moreover, SV-ACS and MV-ACS case-control matched groups were constructed and compared to the MINOCA population. Case-control matching was performed based on diabetes mellitus, current smoking status, presentation with STE-ACS, gender, and age (with a match tolerance of 2 years for the latter) (data not shown). Again, the MINOCA patients showed higher risk of dying compared to SV-ACS, while a comparable risk of dying was found in MV-ACS, which is in line with the multivariable logistic regression analysis.

### 3.2. Outcomes: Other

Although anticoagulant medication was less common in MINOCA patients, there was no difference in the occurrence of bleeding complications between MINOCA and SV-ACS patients. On the contrary, MV-ACS patients had significantly higher occurrence of bleeding at 30 days and 1 year follow-up than MINOCA patients (respectively 23.0% vs. 4.4%,  $p < 0.001$ , and 35.0% vs. 8.2%,  $p < 0.001$ ). Revascularisation procedures were more common in both MICAD groups compared to the MINOCA group. Together, this resulted in a significantly higher prevalence of MACE at 30 days and 1 year follow-up in the SV-ACS and MV-ACS groups compared to MINOCA (Table 4).

## 4. Discussion

We have presented a retrospective analysis of nearly 8000 adult patients admitted and treated for ACS in a large non-academic hospital in the Netherlands. Patient characteristics and outcomes were compared between MINOCA and SV-ACS, as well as between MINOCA and MV-ACS. Although MACE occurred less frequently in patients with MINOCA, the mortality rates in MINOCA patients were intermediate between those of both MICAD groups.

A growing body of literature on MINOCA has increased the awareness amongst physicians that, firstly, the absence of obstructive coronary arteries does not exclude an AMI, and secondly, that AMI without coronary obstruction does not eradicate the need for further diagnostic measures. The underlying mechanisms of MINOCA are diverse [16]. While in some cases additional diagnostic measures reveal the underlying mechanism, e.g., Takotsubo cardiomyopathy, myocarditis, or coronary spasm, no explanation is found in a significant proportion of patients. Hence, both the European Society of Cardiology and American Heart Association proposed to use the term MINOCA as a 'working diagnosis', which should incite further evaluation [2,3]. Whether to use the term MINOCA as an all-encompassing term, or rather to reserve the term for patients in whom an ischemic basis for their clinical presentation is proven, remains debateable [2,3]. Although the underlying diagnosis is not known in the currently presented MINOCA population, all patients met the diagnostic criteria of AMI and required coronary angiography. Accordingly, the results of the present study describe prognosis and outcomes of a general, unselected cohort of AMI patients, which should adequately reflect current practice.

The prevalence of MINOCA in the literature varies from 1 to 15%, which can be partially explained by differences in studied populations and varying definitions of MINOCA used across studies [5,6,17]. In the current study, MINOCA patients, defined as any case of coronary stenosis < 50% determined by coronary angiography [13,18], made up 5.2% of the ACS population, which lies in the reported range consistent with previous studies [1].

The profile of MINOCA patients seems to differ from MICAD patients. For example, several studies report that MINOCA patients are more often female, younger and presenting with NSTEMI-ACS, although contradictions in literature remain [1,8,14,19–23]. Our results clearly show that the MINOCA group holds the largest proportion of female patients (51.5%). In line with previous findings, the proportion of NSTEMI-ACS was largest in the MINOCA group (58.5%). The prevalence of other cardiovascular risk factors including hypertension, hypercholesterolemia, current smoking, and diabetes mellitus in the MINOCA group was in between those of the SV-ACS and MV-ACS groups, suggesting an ‘intermediate’ risk profile to be applicable for this specific AMI group. This observation underlines the importance of considering MINOCA as a separate entity which should not be disregarded in terms of cardiovascular risk. While some studies found risk factors to be less common in MINOCA, other studies found no significant differences in hypertension, dyslipidaemia, and diabetes across groups [10,14,22]. The discrepancies between part of previous studies and the current results could be explained by differences in study population and the fact that in these studies MINOCA was compared to a general MICAD group [14,22]. Except for the study by Kang et al., most previous studies compared the MINOCA patients to a general MICAD group, without discriminating between single and multi-vessel disease [14,21,24,25]. The current results suggest that MINOCA should be viewed as a particular subgroup with a cardiovascular risk profile and concomitant prognosis worse than SV-ACS, but more favourable than MV-ACS. This might explain the failure of several previous observational studies to detect differences between MINOCA and MICAD, depending on the studied composition of MINOCA subdiagnoses, and composition of SV- and MV-ACS [26]. Similarly, previous studies suggesting a favourable prognosis in MINOCA patients compared to a general MICAD group should be interpreted with caution, since overrepresentation of MV-ACS might mask similarities between MINOCA and SV-ACS with respect to clinical outcome parameters.

Although MINOCA patients used less oral anticoagulant medication compared to SV-ACS patients, bleeding complications occurred in similar frequencies in both groups (Table 4). The MV-ACS group, on the other hand, displayed a greater risk of bleeding while the use of anticoagulant therapy was comparable to SV-ACS patients. This might be the result of a different risk profile in MV-ACS, including advanced age. Moreover, CABG was more commonly employed in MV-ACS patients, which could contribute to the occurrence of surgical bleeding complications. Important to note when interpreting these results is that prescription or continuation of DAPT following CABG was not considered common practice at the time of data collection, reflected by the relatively small proportion of patients using DAPT at discharge and follow-up.

Extrapolating the intermediate cardiovascular risk profile found in MINOCA patients, all-cause mortality rates showed to be roughly similar in MINOCA and SV-ACS, but significantly higher in MV-ACS compared to MINOCA. In a multivariable logistic regression model, advanced age, STEMI-ACS, diabetes mellitus, current smoking, and higher creatinine levels at admission appeared to impose a significant contribution to mortality. Taking these factors into account, the odds of dying were lower in SV-ACS patients compared to MINOCA, whereas MINOCA and MV-ACS patients had similar odds. These results are contradictory to Ishii et al., who showed an increased hazard of in hospital and 30 day mortality rates in

MINOCA compared to MICAD. The systematic review by Pasupathy et al., on the other hand, revealed lower odds of in-hospital and 1 year mortality in MINOCA [1,27]. A possible explanation for differences in mortality rates found across studies and contradictions in the direction of these differences can be assigned to the heterogeneity in underlying diseases present in MINOCA. Since a variety of mechanisms can be responsible for induction of MINOCA, future studies should focus on analysing MINOCA subgroups to draw reliable conclusions on prognosis, eventually contributing to improved patient-tailored treatment and follow-up.

With the reveal of MINOCA being a potential risk factor for mortality, clinicians should strive for determining the underlying pathology responsible for the ACS so that appropriate treatments can be initiated. One diagnostic measure to consider in MINOCA is cardiovascular magnetic resonance (CMR) assessment, with benefits including its non-invasive character and the ability to discriminate between myocardial inflammation and fibrosis [4]. Moreover, CMR appears to be safe and effective in the acute phase in AMI patients [28]. A recent study by Dastidar et al. showed that CMR contributes to identification of a definite diagnosis in most MINOCA cases [29]. Revealing the underlying cause provides guidance for the physician to initiate sufficient treatment, as well as additional information on the prognosis of the individual patient.

## 5. Study limitations

For adequate interpretation of the current study results, it is important to take into account the limitations inherent in the observational study design. Data were retrieved based on standard protocols, but physician’s interpretation may have played a role in assessing the coronary obstruction. Given the large time span of data collection, numerous physicians were involved in treating and evaluating patients. Therefore, the results reflect an average of several assessment attitudes, limiting the influence of assessment bias.

Inherent to the timespan of data collection, depicted cardiac troponin values were obtained with both conventional and high sensitive troponin assays. Due to differences in measurement accuracy and thresholds, comparison of different troponin assays is challenging. All troponin values were computed into the same unit (ng/L) for practical reasons. Furthermore, serial troponin values were not available and thus we were unable to detect a (significant) rise and/or fall in troponin values. Hence, we decided to use the more general term ACS instead of the term myocardial infarction.

Although troponin is known to be associated with clinical outcome, troponin values were not included in the current multivariable regression model due to missing data in a large proportion of patients. Moreover, data regarding the underlying diagnosis in MINOCA was not available, precluding analyses of specific MINOCA subtypes. Since the diagnostic work-up applied in MINOCA patients was left at the discretion of the treating cardiologist, no particular diagnostic algorithm was utilised. This work therefore represents an unselected general MINOCA group, reflecting current clinical practice.

Although the maximum follow-up with regards to mortality showed heterogeneity across the study population (inherently to follow-up of mortality), to the best of our knowledge, the current study results represent the longest follow-up time reported to date.

Lastly, a number of commonly used bleeding definitions have been defined following the start of data collection. Since one particular predefined bleeding definition is challenging to translate into another, the decision was made to retain the currently used

bleeding definition, as defined by the research group at the time of initiation of this prospective registry.

## 6. Impact on daily practice

Based on the prevalence of cardiovascular risk factors and translation into substantial mortality rates in MINOCA, the syndrome may no longer be considered benign. Physicians should therefore advocate for adopting adequate follow-up routines and employment of additional diagnostic measures in patients presenting with MINOCA, which might reveal the underlying pathophysiology responsible for the AMI. This will drive patient-tailored treatment, and ultimately, contribute in lowering the risk of recurrent cardiovascular events and death.

## 7. Conclusions

MINOCA patients constitute to a significant proportion of the patients presenting with ACS and show an 'intermediate' risk profile, which translates into slightly higher mortality rates than in SV-ACS, but lower than in MV-ACS patients. Hence, MINOCA should be recognised as a risk factor for mortality, requiring adequate follow-up.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relation which could have affected the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100572>.

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