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ORIGINAL ARTICLE
Coronary artery disease

Sex differences in treatment and outcomes amongst myocardial infarction patients presenting with and without obstructive coronary arteries: a prospective multicentre study

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Aims

Women have an increased prevalence of myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA). Whether sex differences exist in the outcomes of patients with MI and obstructive coronary arteries (MIOCA) vs. MINOCA remains unclear. We describe sex-based differences in diagnosis, treatment, and clinical outcomes of patients with MINOCA vs. MIOCA.

Methods and results

A large-scale cohort study of patients with ST/non-ST elevation MI undergoing coronary angiography (01/2015–12/2019). Patient demographics, diagnosis, prescribed discharge medications, in-hospital complications, and follow-up data were prospectively collected. A total of 13 202 participants were included (males 68.2% and females 31.8%). 10.9% were diagnosed with MINOCA. Median follow-up was 4.62 years. Females (44.8%) were as commonly diagnosed with MINOCA as males (55.2%), unlike the male preponderance in MIOCA (male, 69.8%; female, 30.2%). Less secondary prevention medications were prescribed at discharge for MINOCA than MIOCA. There was no difference in mortality risk between MINOCA and MIOCA [in-hospital: adjusted odds ratio (OR) 1.32, 95% confidence interval (CI) 0.74–2.35, $P = 0.350$; long term: adjusted hazard ratio (HR) 1.03, 95% CI 0.81–1.31, $P = 0.813$]. MINOCA patients had reduced mortality at long-term follow-up if prescribed secondary prevention medications (aHR 0.64, 95% CI 0.47–0.87, $P = 0.004$). Females diagnosed with MIOCA had greater odds of in-hospital and 1-year mortality than males (aOR 1.50, 95% CI 1.09–2.07, $P = 0.014$; aHR 1.18, 95% CI 1.01–1.38, $P = 0.048$).

Conclusion

MINOCA patients have similar mortality rates as MIOCA patients. MINOCA patients were less likely than those with MIOCA to be discharged with guideline-recommended secondary prevention therapy; however, those with MINOCA who received secondary prevention survived longer. Females with MIOCA experienced higher mortality rates vs. males.

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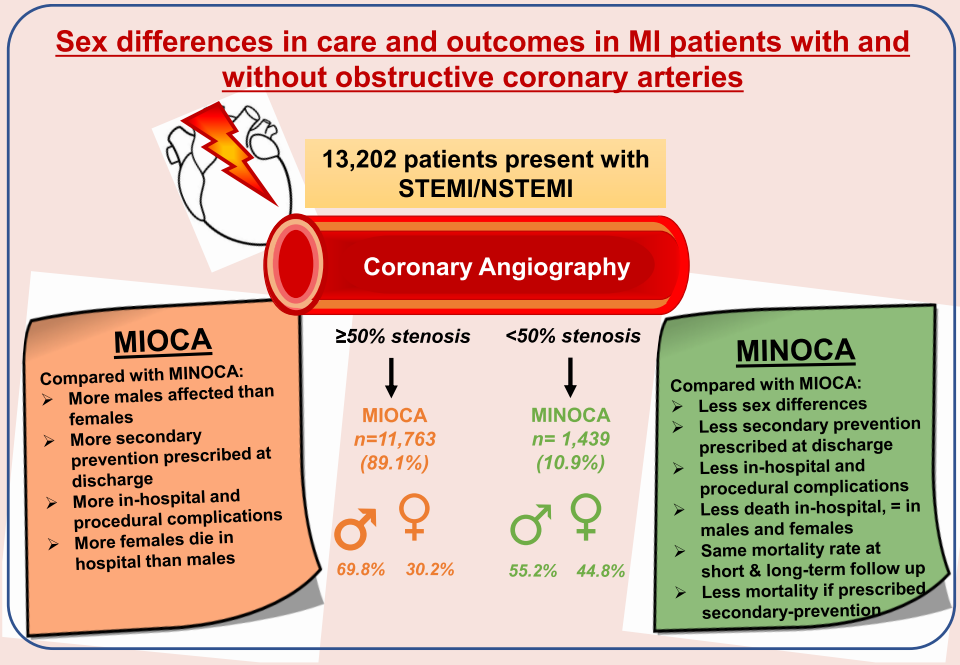
Central Illustration



♂, male; ♀, female; NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; MIOCA, myocardial infarction with obstructive coronary arteries

Keywords Myocardial infarction with non-obstructive coronary arteries (MINOCA) • Myocardial infarction with obstructive coronary arteries (MIOCA) • Acute coronary syndrome • Non-ST elevation myocardial infarction (NSTEMI) • ST elevation myocardial infarction (STEMI)

Introduction

Cardiovascular disease accounts for over four million deaths in Europe annually.[1] Many of these are attributable to acute coronary syndrome (ACS).[2] International guidelines recommend either invasive coronary angiography or non-invasive imaging for patients with ACS, depending on their estimated short-term risk of acute ischaemic events.[2] In approximately 6% of patients with an initial diagnosis of ACS, angiography shows non-obstructive coronary arteries.[3]

A European Society of Cardiology (ESC) working group recommended diagnosing myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) in patients that meet the fourth universal criteria for MI in whom the angiogram shows no stenoses of 50% or greater in a major epicardial vessel and where there is no other alternative cause identified.[4] Patients with MINOCA have heterogeneous underlying pathophysiological mechanisms including plaque rupture/erosion, coronary artery spasm, thromboembolism, spontaneous coronary artery dissection, microvascular dysfunction, takotsubo syndrome, and myocarditis.[5,6] Previous studies have shown that MINOCA is associated with better clinical outcomes than MI with obstructive coronary arteries (MIOCA).[3,7,8]

Females comprise almost 50% of patients with MINOCA compared to approximately 25% of patients with MIOCA.[4] However, females are under-represented in clinical trials,[9,10] and females with MI less frequently receive guideline-indicated clinical care.[11] There are limited data on sex differences in diagnosis, treatment, and long-term clinical outcomes in patients with MINOCA. Therefore, this large-scale prospective study aims to identify and describe sex differences in diagnosis, treatment, and long-term clinical outcomes in patients with MINOCA compared with MIOCA.

Methods

Study design, setting, and participants

A cohort study of patients with a presenting diagnosis of ST or non-ST elevation MI that underwent invasive coronary angiography at the Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK, between 1st of January 2015 and 31st of December 2019 is used in this study. The Freeman Hospital receives patients referred from six district hospitals covering a population of 2 million with an annual percutaneous coronary intervention procedure volume of ~3000 cases (60–65% ACS cases). Participants were classified as having MI with obstructive coronary arteries (MIOCA) if coronary angiography showed a stenosis of ≥50% in the left main stem, left anterior descending coronary artery, right coronary artery, or left circumflex coronary artery or MINOCA if the angiogram showed no stenoses of ≥50% in a major epicardial vessel, according to the ESC Working Group recommendations.[2] In our study, we present MINOCA as a heterogeneous condition based on their presentation and not as a final diagnosis.

Variables and data sources

Baseline data for consecutive admissions with MI were prospectively collected in the British Cardiovascular Intervention Society (BCIS) database for all patients including the full procedural data. Variables include age and sex, indication for angiography, family history of coronary artery disease, smoking status, and history of hypertension, hypercholesterolaemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD),

Table 1 Discharge diagnosis by sex

	Total		Male		Female		*P*-value
	(*n* = 13 202)		(*n* = 9000)		(*n* = 4202)		
Diagnosis and breakdown							
MIOCA, *n* (%)	11763	(89.1)	8205	(69.8)	3558	(30.2)	<0.001
STEMI, *n* (%)	4366	(37.1)	3102	(37.8)	1266	(35.6)	<0.001
NSTEMI, *n* (%)	7397	(62.9)	5103	(62.2)	2292	(64.4)	0.019
MINOCA, *n* (%)	1439	(10.9)	795	(55.2)	644	(44.8)	<0.001
Other diagnosis, *n* (%)	715	(49.7)	441	(55.5)	274	(42.5)	<0.001
Chest pain, unknown cause, *n* (%)	654	(45.4)	346	(43.5)	308	(47.8)	<0.001
Takotsubo cardiomyopathy, *n* (%)	70	(4.9)	8	(1.0)	62	(9.6)	<0.001

MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.

cerebrovascular disease, peripheral vascular disease, heart failure, chronic kidney disease, and previous ischaemic heart disease (angina, MI). Discharge diagnosis and medication details were obtained from the electronic clinical record as listed at the point of discharge.

In-hospital complications were prospectively collected from the patient electronic records, which included all-cause mortality, emergency coronary artery bypass surgery (CABG), stroke, any MI (re-infarction, repeat inpatient MI), cardiac tamponade, any arterial complication, renal failure defined as any acute kidney injury, and any other complication (referral for urgent CABG, requirement for a blood transfusion, required re-intervention, and gastrointestinal bleed). Procedural specific complications include coronary artery perforation or dissection, arterial branch occlusion, direct current cardioversion required during procedure, stent specific complication, cardiogenic shock, and any other (no coronary artery flow, aortic dissection, and heart block).

Long-term follow-up data were collected using the Summary Care Records (SCR), National Health Service (NHS) Digital and tertiary centre hospital electronic patient records. Summary Care Record is an electronic record of important patient information, created from primary care physician medical records. The primary outcome was all-cause mortality censored at 1-year and long-term follow-up. Secondary outcome was first emergency readmission with MI or heart failure at one- and long-term follow-up. Formal ethical approval was not needed for this analysis of routinely collected data.

Statistical methods

The distribution of each variable was examined using histograms. Normally distributed continuous variables are presented as mean and standard deviation (SD) and proportions as count and percentage. Student *t*-test was used to compare continuous variables and chi-square (χ^2) or Fisher's exact test for proportions. Non-normally distributed data were analysed using non-parametric tests including Wilcoxon rank sum test.

Stepwise logistic regression with backwards elimination was used to analyse the association between discharge diagnosis, sex, and all-cause mortality. All variables included in the baseline descriptive statistics were included in the initial pool of variables and were eliminated based on a *P*-value threshold of $P < 0.05$. Adjusted odds ratio (OR) and hazard ratio (HR) estimates with 95% confidence interval (CI) were reported for the final retained variables used in the regression models, which include age, family history of coronary artery disease, hypercholesterolaemia, hypertension, smoking status, cardiogenic shock at the time of angiogram, and ST-segment elevation on baseline ECG. Secondary regression analysis was used to analyse the effect of prescribed discharge medications on mortality, regression models were generated using the variables above in combination with any prescribed discharge medications [angiotensin-converting enzyme (ACE) inhibitor/ angiotensin receptor blocker (ARB), aldosterone antagonist, aspirin, beta-blockers, clopidogrel/prasugrel, ticagrelor, statin]. Stepwise model coefficients were tested using chi-square tests, and goodness of fit and proportionality of hazards were checked to test the regression models used. Cumulative survival for longer-term follow-up was described for patients stratified by diagnosis (MINOCA and MIOCA) and sex category (males and females). The log–rank rest was used to assess difference in mortality. SPSS 27 (IBM, USA) was used for all analyses. A *P*-value <0.05 was considered statistically significant.

Results

Participants and discharge diagnosis

There were 13 202 participants included in this study: 9000 males (68.2%), mean age (SD) 68 (12) years and 4202 females (31.2%), mean age (SD) 73 (13) years. Median follow-up duration was 4.62 years. A diagnosis of NSTEMI (7397, 62.9%) was more frequent than STEMI (4366, 37.1%) for patients diagnosed with MIOCA. Females were less frequently diagnosed with both NSTEMI and STEMI than males.

Of these, 1439 (10.9%) were diagnosed with MINOCA and 11 763 (89.1%) with MIOCA (*Table 1*). There was a smaller but still significant male to female sex difference in those diagnosed with MINOCA (males 55.2% and females 44.8%) than MIOCA (males 69.8% and females 30.2%). Of patients diagnosed with MINOCA, 715 (49.7%) had a documented discharge diagnosis of 'other diagnosis' and 654 (45.4%) of 'chest pain, unknown cause'. A diagnosis of 'other diagnosis' was given more frequently to males (55.5% vs. 42.5%, $P < 0.001$), and a diagnosis of 'chest pain, unknown cause' was given more frequently to females (47.8% vs. 43.5%, $P < 0.001$). In 70 (4.9%) patients diagnosed with MINOCA, takotsubo syndrome was confirmed prior to discharge, a diagnosis which was more common in females than males (9.6% vs. 1%; $P < 0.001$).

Baseline characteristics by discharge diagnosis

Females were on average older than males in patients diagnosed with MINOCA [mean (SD), 69 (12.9) vs. 64 (14.6) years, $P < 0.001$] and MIOCA [74 (12.8) vs. 69 (12.2) years, $P < 0.001$] (*Table 2*). The most common initial indication for angiography was NSTEMI (66%), a presentation seen more frequently in females diagnosed with MINOCA than MIOCA (84% vs. 65.9%). Patients diagnosed with MINOCA had fewer risk factors for coronary artery disease than those diagnosed with MIOCA (hypertension 38% vs. 59%, $P < 0.001$; hypercholesterolaemia 23% vs. 48%, $P < 0.001$; diabetes 14% vs. 24%, $P < 0.001$).

The frequency of risk factors for cardiovascular disease was similar between males and females in those diagnosed with MINOCA.

Table 2 Sex differences stratified by diagnosis

		MIOCA (n = 11 763)				P-value	MINOCA (n = 1439)				P-value
		Male		Female			Male		Female		
Age, years (SD)		69	(12.2)	74	(12.8)	**<0.001**	64	(14.6)	69	(12.9)	**<0.001**
Indication for angiography											
STEMI, *n* (%)		3021	(36.0)	1235	(34.1)	<0.001	146	(24.3)	91	(16.0)	<0.001
NSTEMI, *n* (%)		5361	(64.0)	2389	(65.9)	0.035	456	(75.7)	478	(84.0)	<0.001
Social demographics											
Family history CAD, *n* (%)		3487	(45.7)	1452	(44.8)	0.357	158	(25.7)	100	(21.1)	0.078
Smoking status	Non-smoker, *n* (%)	2531	(32.5)	1379	(41.4)	<0.001	289	(46.8)	257	(53.0)	0.043
	Ex-smoker, *n* (%)	3214	(41.3)	1116	(33.5)	<0.001	211	(34.2)	155	(32.0)	0.087
	Smoker, *n* (%)	2043	(26.2)	835	(25.1)	<0.001	117	(19.0)	73	(15.1)	0.078
Past medical history											
HTN, *n* (%)		4731	(58.7)	2247	(65.3)	<0.001	308	(44.1)	246	(46.8)	0.346
Hypercholesterolaemia, *n* (%)		3933	(48.8)	1722	(50.0)	0.240	185	(26.5)	145	(27.6)	0.667
DM, *n* (%)		1916	(24.0)	924	(27.1)	<0.001	123	(18.1)	83	(16.1)	0.356
COPD, *n* (%)		742	(9.3)	440	(13.0)	<0.001	69	(10.5)	79	(15.6)	0.010
CVD, *n* (%)		561	(7.0)	185	(5.4)	<0.001	27	(3.9)	12	(2.3)	0.334
PVD, *n* (%)		535	(6.6)	290	(8.4)	<0.001	48	(6.9)	29	(5.5)	0.119
HF, *n* (%)		216	(2.7)	96	(2.8)	0.002	20	(2.9)	16	(3.0)	0.853
Valve disease, *n* (%)		80	(1.0)	20	(0.6)	0.092	4	(0.6)	6	(1.2)	0.694
CKD, *n* (%)		73	(0.9)	43	(1.2)	0.031	10	(1.4)	9	(1.7)	0.280
Previous ischaemic heart Disease											
Angina, *n* (%)		2658	(33.3)	1053	(31.0)	0.016	171	(25.8)	96	(19.2)	0.008
MI, *n* (%)		2264	(28.3)	809	(23.8)	<0.001	143	(21.6)	67	(13.4)	<0.001
Procedural characteristics											
Arterial access	Radial, *n* (%)	7388	(90.2)	2991	(84.3)	<0.001	734	(92.6)	571	(88.7)	0.093
	Femoral, *n* (%)	777	(9.5)	540	(15.2)	<0.001	56	(7.1)	71	(11.0)	*0.025*
	Other, *n* (%)	28	(0.3)	18	(0.5)	0.404	3	(0.4)	2	(0.3)	0.467
Cardiogenic shock pre-angio, *n* (%)		210	(2.7)	118	(3.6)	0.012	14	(2.3)	4	(0.9)	0.071
IVUS, *n* (%)		561	(4.8)	220	(1.9)	*0.713*	6	(0.4)	6	(0.4)	0.900

MIOCA, myocardial infarction with obstructed coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; SD, standard deviation; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CVD, Cerebrovascular disease; PVD, peripheral vascular disease; HF, heart failure; CKD, chronic kidney disease; MI, myocardial infarction; CABG, coronary artery bypass graft; pre-angio, pre-angiogram; IVUS, intravascular ultrasound.

Females diagnosed with MIOCA more commonly had risk factors for cardiovascular disease than males including hypertension and diabetes mellitus. Females diagnosed with MIOCA also tended to have a greater comorbidity burden (including COPD, peripheral vascular disease, heart failure, and chronic kidney disease) than males.

Procedural characteristics by discharge diagnosis

Angiography was performed via the radial artery in 89% of patients (*Table 2*). Femoral access was used more frequently in females compared to males in MIOCA (9.5% vs. 15%). Intravascular ultrasound (IVUS) was used less frequently in patients diagnosed with MINOCA than MIOCA (0.4% vs. 2%). Cardiogenic shock at the time of the angiogram was less common in patients diagnosed with MINOCA than MIOCA (1.3% vs. 2.8%) and more common in females diagnosed with MIOCA than males (3.6% vs. 2.7%, $P = 0.012$).

Complications by discharge diagnosis

Patients diagnosed with MINOCA experienced fewer in-hospital complications (2.8% vs. 5.1%, $P < 0.05$) and fewer procedural complications (0.9% vs. 3%) than MIOCA (*Table 3*). There was a greater frequency of procedural complications in females diagnosed with MIOCA than males (4.1% vs. 2.9%, $P < 0.001$). Coronary artery perforation or dissection was the most common procedural complication and was more common in females than males diagnosed with MIOCA (females 2.3% and males 1.2%; $P = 0.004$).

Discharge medications by discharge diagnosis

Table 4 shows the most commonly prescribed discharge medications given to patients post-MI. Patients with MIOCA were most frequently prescribed an ACEi/ARB (89.1%), aspirin (94.9%), beta-blocker (88.3%), and statin (93.4%). All patients were prescribed aldosterone antagonists and a second anti-platelet agent to a lesser extent.

Table 3 In-hospital and procedural complications and sex differences stratified by diagnosis

		MIOCA				*P*-value	MINOCA				*P*-value
		Male		Female			Male		Female		
		n = 8062		*n* = 3486			*n* = 783		*n* = 635		
In-hospital complications											
In-hospital complications (all cause)		386	(4.8)	210	(6.0)	0.008	27	(3.4)	13	(2.0)	0.082
Complications	All-cause mortality	171	(2.1)	113	(3.2)	<0.001	19	(2.4)	10	(1.6)	0.281
	Emergency CABG	12	(0.1)	7	(0.2)	0.710	2	(0.3)	0	—	—
	Stroke	7	(0.1)	14	(0.4)	0.025	1	(0.1)	0	—	—
	MI	7	(0.1)	2	(0.1)	0.288	0	—	1	(0.2)	—
	Tamponade	4	(0.0)	6	(0.2)	0.040	0	—	0	—	—
	Arterial complication	4	(0.0)	1	(0.0)	0.369	0	—	0	—	—
	Renal failure	3	(0.0)	2	(0.1)	0.992	0	—	0	—	—
	Any other	178	(2.2)	65	(1.9)	<0.001	5	(0.6)	2	(0.3)	0.22
Procedural complications											
Procedural complications (all cause)		231	(2.9)	142	(4.1)	<0.001	6	(0.8)	6	(0.9)	0.304
Complications	Perforation/dissection	99	(1.2)	83	(2.4)	0.004	3	(0.4)	0	—	—
	Side branch occlusion	27	(0.3)	9	(0.3)	0.287	1	(0.1)	1	(0.2)	0.687
	DCCV required	11	(0.1)	8	(0.2)	0.117	0	—	0	(0.0)	—
	Stent complication	9	(0.1)	2	(0.1)	0.012	0	—	0	(0.0)	—
	Shock	2	(0.0)	1	(0.0)	0.571	0	—	1	(0.2)	—
	Any other	83	(1.0)	39	(1.1)	0.009	2	(0.3)	4	(0.6)	0.058

MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; CABG, coronary artery bypass surgery; MI, myocardial infarction; DCCV, direct current cardioversion. (—) represents inability to test for significant differences due to one or more variables containing zero count.

Females diagnosed with MIOCA were prescribed all discharge medications less frequently than males ($P < 0.02$). All discharge medications recorded were prescribed less frequently for patients with MINOCA than MIOCA ($P < 0.05$). Patients with MINOCA were also most commonly prescribed an ACEi/ARB (56.5%), aspirin (42.8%), beta-blocker (54.8%), and statin (59.3%). Aspirin was prescribed less frequently to females with MINOCA (females 39% and males 46.6%, $P = 0.008$); there were no other significant differences in prescribed discharge medications between males and females with MINOCA.

Readmission rate by discharge diagnosis

The number of emergency first readmissions for MI or heart failure at 1 year was not statistically different between males and females, for those diagnosed with MIOCA (males 5.7% and females 5.8%) and MINOCA (males 5.0% and females 4.2%) (*Table 5*). Likewise, there was no difference observed in the readmission rate between males and females at long-term follow-up for MIOCA (males 12.4% and females 12.6%) and MINOCA patients (males 10.1% and females 7.9%).

Mortality by discharge diagnosis

Amongst those diagnosed with MIOCA, in-hospital all-cause mortality was significantly higher in females than males (3.2% vs. 2.1%; $P < 0.001$, *Table 3*). Females diagnosed with MIOCA were more likely to die following discharge from hospital, observed at both 1-year (mortality: males 6.9% and females 9.2%, $P < 0.001$) and at long-term follow-up (mortality: males 11.2% and females 14.2%, $P < 0.001$) (*Table 5*). There was no significant difference in all-cause mortality between males and females in those diagnosed with MINOCA in-hospital (1.6% vs. 2.4%, *Table 3*) and during 1-year and long-term follow-ups (*Table 5*).

The odds of in-hospital mortality in those diagnosed with MINOCA was not significantly different from those diagnosed with MIOCA (adjusted OR 1.32, 95% CI 0.74–2.35, $P = 0.350$) (*Table 6*). There was no significant difference in the risk of mortality for patients diagnosed with MINOCA compared to MIOCA at 1-year (adjusted HR 1.21, 95% CI 0.91–1.62, $P = 0.188$) and at long-term follow-up (adjusted HR 1.03, 95% CI 0.81–1.31, $P = 0.813$). Males with MINOCA were more at risk of dying than those with MIOCA during longer-term follow-up (adjusted HR 1.52, 95% CI 1.11–2.07, $P = 0.009$).

Patients diagnosed with MINOCA had a significantly reduced risk of mortality than MIOCA when adjusted to include prescribed discharge medications at 1-year (adjusted HR 0.61, 95% CI 0.42–0.90, $P = 0.012$) and at long-term follow-up (adjusted HR 0.64, 95% CI 0.47–0.87, $P = 0.004$). Females diagnosed with MINOCA had a significantly reduced risk of mortality than those with MIOCA when adjusted to include prescribed discharge medications at 1-year (adjusted HR 0.45, 95% CI 0.24–0.83, $P = 0.011$) and at long-term follow-up (adjusted HR 0.38, 95% CI 0.23–0.63, $P = 0.001$). Without adjustment for discharge medication, females diagnosed with MINOCA had no significant differences in the risk of dying at 1-year and longer-term follow-up compared to those with MIOCA.

Females diagnosed with MIOCA had 50% greater odds of in-hospital mortality than males (adjusted OR 1.50, 95% CI 1.09–2.07, $P = 0.014$) (*Table 7*), also seen at 1-year of follow-up (adjusted HR 1.18, 95% CI 1.01–1.38, $P = 0.048$). There was no significant difference in the adjusted risk of mortality for long-term follow-up for females diagnosed with either MIOCA or MINOCA. There was no effect of adjusting for prescribed discharge medication on the risk of mortality in females compared to males for either diagnosis group.

Table 4 Discharge medications and sex differences stratified by diagnosis

	MIOCA				*P*-value	MINOCA				*P*-value
	Male		Female			Male		Female		
	n = 7826		*n* = 3383			*n* = 678		*n* = 543		
Discharge medication										
ACEi/ARB, *n* (%)	7171	(91.2)	2939	(86.9)	<0.001	377	(55.6)	313	(57.6)	0.475
Aldosterone antagonist, *n* (%)	586	(7.5)	196	(5.8)	0.002	44	(6.5)	22	(4.1)	0.061
Aspirin, *n* (%)	7548	(96.0)	3176	(93.9)	<0.001	316	(46.6)	212	(39.0)	0.008
Beta-blocker, *n* (%)	7016	(89.2)	2956	(87.4)	0.004	381	(56.2)	290	(53.4)	0.331
Clopidogrel/prasugrel, *n* (%)	4217	(53.6)	1655	(48.9)	<0.001	120	(17.7)	81	(14.9)	0.193
Ticagrelor, *n* (%)	3246	(41.3)	1477	(43.7)	0.019	42	(6.2)	31	(5.7)	0.722
Statin, *n* (%)	7448	(94.7)	3114	(92.0)	<0.001	411	(60.6)	315	(58.0)	0.356

MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 5 Follow-up and outcomes and sex differences stratified by diagnosis

	MIOCA				*P*-value	MINOCA				*P*-value
	Male		Female			Male		Female		
	n = 8203		*n* = 3558			*n* = 795		*n* = 644		
Follow-up										
Mean, *years (SEM)*	4.79	(0.02)	4.82	(0.02)	0.303	4.64	(0.05)	4.62	(0.06)	0.779
Median, *years (SD)*	4.71	(1.48)	4.8	(1.48)	0.190	4.48	(1.39)	4.52	(1.40)	0.773
Emergency first readmission[a]										
One-year, *n* (%)	465	(5.7)	207	(5.8)	0.749	40	(5.0)	27	(4.2)	0.453
Long-term, *n* (%)	1020	(12.4)	450	(12.6)	0.748	80	(10.1)	51	(7.9)	0.160
Mortality rate										
One-year, *n* (%)	564	(6.9)	327	(9.2)	<0.001	60	(7.5)	42	(6.5)	0.451
Long-term, *n* (%)	915	(11.2)	505	(14.2)	<0.001	81	(10.2)	70	(10.9)	0.970

MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; SEM, standard error of the mean; SD, standard deviation.
[a]For heart failure and myocardial infarction.

Long-term survival

Cumulative survival curves (*Figure 1*) show that there was no statistical difference in the cumulative survival of males and females diagnosed with MINOCA throughout the follow-up period. Females had greater cumulative mortality than males following a diagnosis of MIOCA throughout the follow-up period, $P < 0.001$. Females diagnosed with MIOCA vs. those diagnosed with MINOCA had a significantly reduced cumulative survival at the end of the follow-up period, $P = 0.013$. There was no significant difference in the mortality of males diagnosed with MIOCA or MINOCA at long-term follow-up.

Discussion

The seminal findings of this large-scale study are as follows:

(1) One in 10 patients with a presenting diagnosis of MI had MINOCA. Females were as commonly diagnosed with MINOCA as males, unlike the male preponderance in MIOCA.
(2) Patients diagnosed with MINOCA were younger than those with MIOCA and were less likely than those with MIOCA to be discharged with guideline-recommended secondary prevention therapy.
(3) Patients diagnosed with MINOCA less commonly experienced in-hospital complications than MIOCA. In-hospital and long-term mortality in those diagnosed with MINOCA was not significantly different from those diagnosed with MIOCA.
(4) Patients diagnosed with MINOCA who received secondary prevention medication at discharge were more likely to survive short- and longer-term follow-up.
(5) Females diagnosed with MIOCA are more likely than males to die in-hospital and within 1-year post-discharge (Central Illustration).

Multiple previous studies have reported a frequency of MINOCA diagnosis between 6% and 15% of MI presentations.[3,12,13] Many have also reported that patients diagnosed with MINOCA are younger[5] and that females are more likely to be diagnosed with MINOCA.[4,7] In our study, there is a smaller sex difference in those patients diagnosed with MINOCA vs. those with MIOCA. This reduced sex

Table 6 Mortality in patients with MINOCA compared to MIOCA (reference group) by sex

In-hospital	Unadjusted odds ratio (OR)			Adjusted OR[a]		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
All	1.06	(0.75–1.49)	0.741	1.32	(0.74–2.35)	0.350
Male	1.40	(0.91–2.12)	0.125	1.60	(0.71–3.65)	0.260
Female	0.66	(0.38–1.16)	0.150	1.04	(0.46–2.35)	0.934

	Unadjusted hazard ratio (HR)			Adjusted HR[a]			Adjusted HR[b]		
One-year	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
All	1.13	(0.92–1.38)	0.257	1.21	(0.91–1.62)	0.188	0.61	(0.42–0.90)	**0.012**
Male	1.37	(1.04–1.79)	**0.021**	0.69	(0.48–1.01)	0.053	0.85	(0.52–1.38)	0.506
Female	0.88	(0.63–1.21)	0.414	1.11	(0.71–1.75)	0.659	0.45	(0.24–0.83)	**0.011**
Long-term									
All	1.09	(0.93–1.30)	0.274	1.03	(0.81–1.31)	0.813	0.64	(0.47–0.87)	**0.004**
Male	1.43	(1.14–1.79)	**0.002**	1.52	(1.11–2.07)	**0.009**	1.08	(0.74–1.58)	0.690
Female	0.87	(0.69–1.14)	0.344	0.70	(0.48–1.03)	0.069	0.38	(0.23–0.63)	**<0.001**

OR, odds ratio; HR, hazard ratio; CI, confidence interval; MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries.
[a]Adjusted for age, family history of coronary artery disease, hypercholesterolaemia, hypertension, smoking status, cardiogenic shock at the time of angiogram, and ST-segment elevation on baseline ECG.
[b]Adjusted for as adjustments above, plus any prescribed discharge medication (ACE inhibitor/ARB, aldosterone antagonist, aspirin, beta-blockers, clopidogrel/prasugrel, ticagrelor, statin).

Table 7 Mortality in females compared to males (reference group) by diagnosis

In-hospital	Unadjusted odds ratio (OR)			Adjusted OR[a]		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
All	1.38	(1.12–1.73)	**0.004**	1.47	(1.08–2.01)	**0.015**
MIOCA	1.51	(1.19–1.91)	**0.001**	1.50	(1.09–2.07)	**0.014**
MINOCA	0.71	(0.37–1.39)	0.322	1.24	(0.37–4.19)	0.725

	Unadjusted hazard ratio (HR)			Adjusted HR[a]			Adjusted HR[b]		
One-year	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
All	1.05	(0.92–1.19)	0.493	1.15	(0.99–1.34)	0.077	1.14	(0.96–1.36)	0.147
MIOCA	1.09	(0.95–1.25)	0.208	1.18	(1.00–1.38)	**0.048**	1.18	(0.98–1.41)	0.084
MINOCA	0.70	(0.47–1.04)	0.078	0.86	(0.48–1.52)	0.602	0.78	(0.32–1.89)	0.585
Long-term									
All	0.98	(0.88–1.09)	0.693	1.05	(0.93–1.18)	0.459	1.05	(0.91–1.20)	0.521
MIOCA	1.02	(0.91–1.35)	0.755	1.09	(0.97–1.25)	0.141	1.10	(0.96–1.27)	0.173
MINOCA	0.68	(0.49–0.94)	**0.021**	0.69	(0.42–1.15)	0.155	0.64	(0.32–1.28)	0.209

OR, odds ratio; HR, hazard ratio; CI, confidence interval; MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries.
[a]Adjusted for age, family history of coronary artery disease, hypercholesterolaemia, hypertension, smoking status, cardiogenic shock at the time of angiogram, and ST-segment elevation on baseline ECG.
[b]Adjusted for as adjustments above, plus any prescribed discharge medication (ACE inhibitor/ARB, aldosterone antagonist, aspirin, beta-blockers, clopidogrel/prasugrel, ticagrelor, and statin).

difference has been described previously, suggesting that more females are likely to have MINOCA overall.[3,6,7,14] As females have a higher prevalence of MINOCA compared to MIOCA, yet the rates of mortality are just as high in both groups, especially in women, clinicians should be cautious in thorough evaluation and treatment of MINOCA in females.

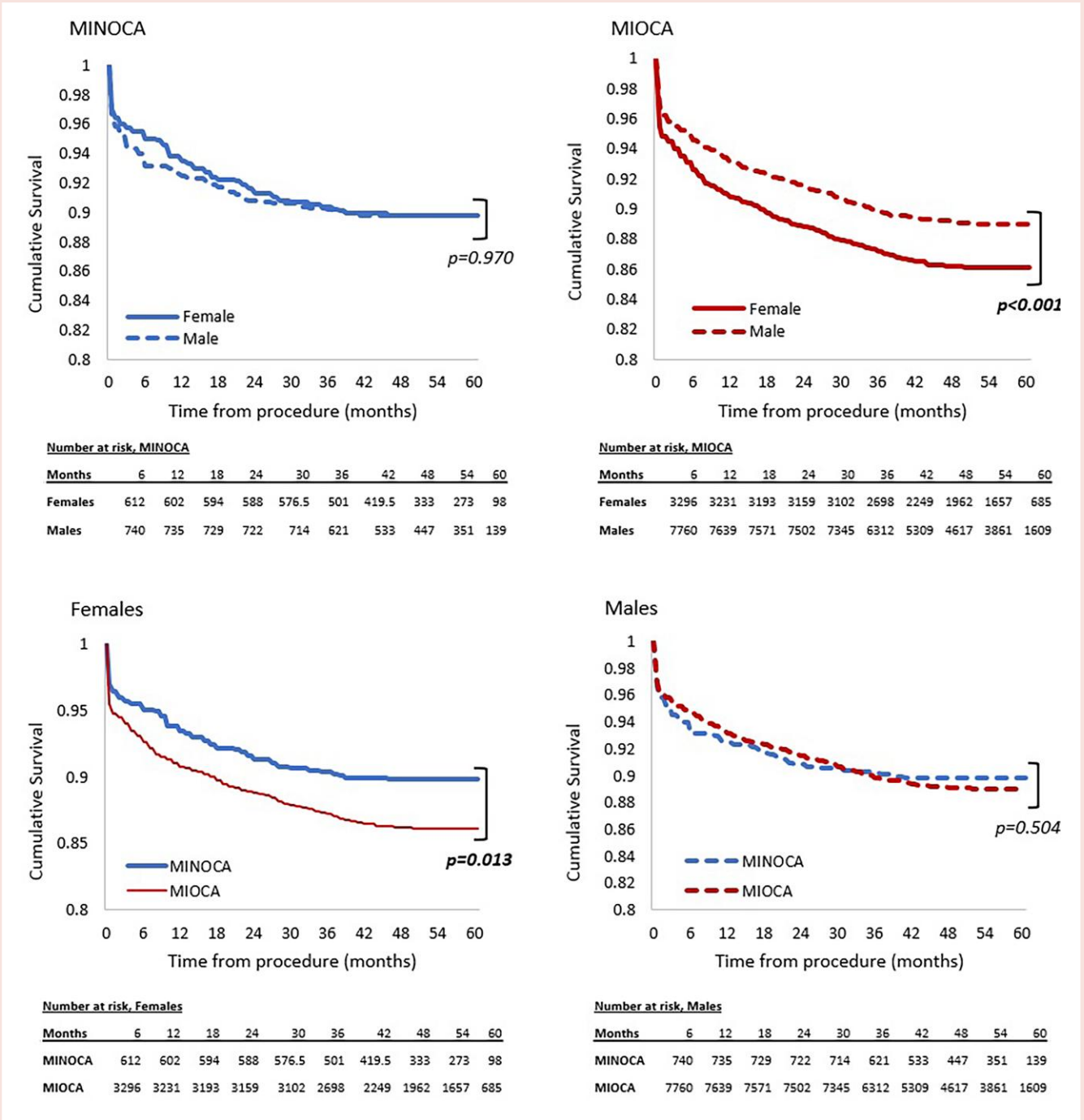


Figure 1 Long-term survival, stratified by diagnosis and sex. MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries.

Presentation with NSTEMI accounts for two-thirds of cases of acute MI presentations in this study and over three-quarters of patients diagnosed with MINOCA, as seen previously.[15] Females diagnosed with MINOCA presented with NSTEMI with much greater frequency than males. The frequency of cardiogenic shock was lower in patients with MINOCA vs. MIOCA, which was observed in low rates in females diagnosed with MINOCA vs. males. Such differences in clinical status at the time of acute presentation may explain why females diagnosed with MINOCA have better in-hospital survival than those diagnosed with MIOCA, as previously reported.[7]

Fewer discharge medications were prescribed to patients with a diagnosis of MINOCA. A recent comparison of patients with MINOCA and medically managed MIOCA also saw a similar discrepancy in the prescription of cardio-protective medications at discharge.[16] We found that <60% of the patients with MINOCA were prescribed cardiovascular risk-limiting medical therapies, whereas >80% of patients diagnosed with MIOCA were. Furthermore, we

have observed that females diagnosed with MIOCA received significantly fewer discharge medications than men, a trend recently observed in a Europe-wide study.[17] We have recently shown that if females and males are provided with guideline-recommended therapy equally, then the long-term outcomes are similar between the sexes.[18]

Previous studies have shown that plaque rupture and erosion were identified in 47% of patients diagnosed with MINOCA, highlighting the importance of secondary prevention in this cohort.[19] Secondary prevention in both male and female patients with MINOCA with statins and ACEi/ARB was associated with significantly reduced adverse outcomes (including all-cause mortality, further MI-related hospitalization, and heart failure).[20] A recent study has shown that patients with MINOCA and higher baseline cholesterol levels have 17% higher incidence of major adverse cardiovascular events at 3.5 years, which further strengthens this argument for optimal secondary prevention following MINOCA.[21]

This study has shown that patients discharged from hospital with a preliminary diagnosis of MINOCA have a 39% greater chance of survival if they are discharged from hospital with cardiovascular modifying secondary prevention therapies. Females with MINOCA discharged with secondary prevention are shown here to have a 55% increased chance survival in the short and long term than females with MIOCA. Taken together, this further reiterates the importance of cardiovascular risk modification in a vulnerable group of patients who are often not treated as per guidelines. Currently there are no clinical trials available to develop guideline directed therapies MINOCA. Further studies are needed to determine whether beta-blockers and ACEi/ARB therapies impact hospitalization rate and mortality of patients with MINOCA.[22]

We have observed no difference in the odds of mortality in-hospital, at 1-year and at long-term follow-up for patients diagnosed with MINOCA and MIOCA. Others have observed a similar rate of 2–3% for in-hospital mortality for patients with MINOCA and MIOCA.[3,7,8,23] A previous meta-analysis consisting of data from both registries and clinical trials reported 12-month all-cause mortality differences between MINOCA and MIOCA (3.3% vs. 5.6%) which might be due to differences in study populations and sample size.[24] MINOCA patients may also experience similar rates of re-hospitalization, angina, and depression as compared to MIOCA patients.[25] In our study, patients diagnosed with MINOCA have a similar rate of readmission to those diagnosed with MIOCA, with no sex difference observed. This further emphasizes that MINOCA is not a benign condition. As MINOCA is a working diagnosis, follow-up and further planned investigation is an important part of the discharge management plan. In concordance with previous studies, we show no difference between clinical outcomes including in-hospital, 1-year, and long-term mortality and re-hospitalization rate for both males and females diagnosed with MINOCA.[26]

In the present study, females with MIOCA have higher adjusted odds of in-hospital mortality and a reduced cumulative survival at 1-year and over long-term follow-up than males. We saw no difference in the adjusted odds of mortality for females diagnosed with MIOCA at long term, consistent with others with longer-term follow-up up to 10 years.[27] As observed previously,[11,17,28,29] this study supports the finding that in the context of MIOCA, females have a greater risk factor and comorbidity burden and are less commonly prescribed secondary prevention pharmacotherapy than males, which may contribute to these findings.

Study strengths and limitations

To our knowledge, this is the first large-scale report to address the comparative sex differences at short- and long-term follow-up in patients diagnosed with MINOCA compared with MIOCA patients. Other strengths include the robust and extensive reporting of demographic, procedural, and outcome data from this large sample of patients with long-term follow-up. However, we acknowledge potential limitations of our work. Firstly, the diagnosis of MINOCA based on clinical and angiographic parameters as per the ESC consensus document made by the cardiologist at the time of the procedure is a working diagnosis with limited use of IVUS, optical coherence tomography, or other functional assessments in our study. On the other hand, our study reflects real-life practice and emphasizes the need for a streamlined diagnostic algorithm for such patients. Patients with 'chest pain, unknown cause' likely have been referred for outpatient evaluation, for example, with echocardiography, cardiac magnetic resonance imaging, and other investigations. Details of the final diagnosis are not available for our patients. However, our study findings provide important insights into the long-term outcomes of MINOCA patients, and worryingly their outcomes are similar to MIOCA patients emphasizing the utmost need to investigate these patients better with a view to initiating appropriate therapy.

Conclusion

In this large-scale study, those diagnosed with MINOCA than MIOCA were less commonly discharged with secondary prevention therapy, which is shown to negatively impact on long-term survival. Despite fewer in-hospital complications, when adjusted for confounders, the odds of dying in-hospital or during follow-up are similar for patients with MINOCA and MIOCA. Females with MIOCA experienced higher mortality rates vs. males. These findings underscore the need for clinicians to be aware that especially female patients diagnosed with MINOCA and MIOCA must be provided with appropriate diagnostic workup and secondary prevention therapy to reduce the mortality in the short and long term.

Data statement

Data will be available on request to the corresponding author.

Author contributions

M.L. undertook data analysis and wrote the first draft and multiple revisions. V.K. conceived the idea and undertook multiple revisions. C.W., Y.A., H.R., C.A., E.P.N., and J.B. provided critical review of the manuscript.

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