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CLINICAL RESEARCH
Coronary artery disease

Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population

Rachel P. Dreyer[1,2]*, Rosanna Tavella [3,4,5], Jeptha P. Curtis[1,6], Yongfei Wang[1,6], Sivabaskari Pauspathy[3,4,5], John Messenger [7], John S. Rumsfeld[7], Thomas M. Maddox[8], Harlan M. Krumholz [1,6,9], John A. Spertus[10], and John F. Beltrame [3,4,5]

[1]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, 1 Church Street, Suite 200, New Haven, Connecticut, USA; [2]Department of Emergency, Yale School of Medicine, 464 Congress Ave, Suite 260, New Haven, Connecticut, 06510, USA; [3]The Queen Elizabeth Hospital, Discipline of Medicine, University of Adelaide, 28 Woodville Road, Woodville South, 5011, South Australia; [4]Basil Hetzel Institute for Translational Research, 37 Woodville Road, Woodville South, 5011, South Australia; [5]Cardiology Department, Central Adelaide Local Health Network, 28 Woodville Road, Woodville South, 5011, South Australia; [6]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, 330 Cedar St, New Haven, 06520-8056, Connecticut, USA; [7]Division of Cardiology, Department of Medicine, University of Colorado School of Medicine, 13001 E 17th Pl, Aurora, Colorado, 80045, USA; [8]Division of Cardiology, Washington University School of Medicine; Healthcare Innovation Lab, BJC HealthCare/Washington University School of Medicine; 660 S Euclid Ave, St Louis, Missouri, 63110, USA; [9]Department of Health Policy and Management, Yale University School of Public Health, 60 College St, New Haven, 06510, Connecticut, USA; and [10]Health Outcomes Research, Saint Luke's Mid America Heart Institute/University of Missouri-Kansas City, 4401 Wornall Rd, Kansas City, Missouri, 64111, USA

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Aims The prognosis of patients with MINOCA (myocardial infarction with non-obstructive coronary arteries) is poorly understood. We examined major adverse cardiac events (MACE) defined as all-cause mortality, re-hospitalization for acute myocardial infarction (AMI), heart failure (HF), or stroke 12-months post-AMI in patients with MINOCA versus AMI patients with obstructive coronary artery disease (MICAD).

Methods and results Multicentre, observational cohort study of patients with AMI (≥65 years) from the National Cardiovascular Data Registry CathPCI Registry (July 2009–December 2013) who underwent coronary angiography with linkage to the Centers for Medicare and Medicaid (CMS) claims data. Patients were classified as MICAD or MINOCA by the presence or absence of an epicardial vessel with ≥50% stenosis. The primary endpoint was MACE at 12 months, and secondary endpoints included the components of MACE over 12 months. Among 286 780 AMI admissions (276 522 unique patients), 16 849 (5.9%) had MINOCA. The 12-month rates of MACE (18.7% vs. 27.6%), mortality (12.3% vs. 16.7%), and re-hospitalization for AMI (1.3% vs. 6.1%) and HF (5.9% vs. 9.3%) were significantly lower for MINOCA vs. MICAD patients ($P < 0.001$), but was similar between MINOCA and MICAD patients for re-hospitalization for stroke (1.6% vs. 1.4%, $P = 0.128$). Following risk-adjustment, MINOCA patients had a 43% lower risk of MACE over 12 months (hazard ratio = 0.57, 95% confidence interval 0.55–0.59), in comparison to MICAD patients. This pattern was similar for adjusted risks of the MACE components.

Conclusion This study confirms an unfavourable prognosis in elderly patients with MINOCA undergoing coronary angiography, with one in five patients with MINOCA suffering a major adverse event over 12 months.

Keywords Myocardial infarction with non-obstructive coronary arteries • AMI and obstructive coronary disease • Prognosis • Clinical outcomes

* Corresponding author. Tel: +1 203 737 7644, Fax: +1 203 764 7356, Email: rachel.dreyer@yale.edu

Introduction

In patients with acute myocardial infarction (AMI), and no evidence of obstructive coronary artery disease (CAD), the underlying cause of the AMI is not always apparent. This ambiguity has prompted clinical researchers to coin the term 'myocardial infarction with non-obstructive coronary arteries' (MINOCA) in order to stimulate systematic research into the area.[1–3] MINOCA encompasses an intriguing group of patients, usually younger and with a different sex distribution than those with obstructive CAD. Several key questions remain unanswered, in particular, do they have the same prognosis as those patients with AMI and obstructive coronary disease (MICAD) and thus managed with the same therapeutic paradigm despite the angiographic findings? However, if their prognosis differs, is it appropriate to institute the same treatment guidelines when there is no evidence that MINOCA patients derive benefit from these therapies?

In relation to prognosis, a recent systematic review identified only a small number of comparative studies revealing a 12-month all-cause mortality rate of 3.5% in MINOCA compared with 6.7% for patients with MICAD.[4] MINOCA is now recognized as a distinct entity,[5] and therefore, a comprehensive understanding of prognosis is needed. The majority of prognostic studies report in-hospital and 12-month mortality between MINOCA and MICAD,[6,7] but relatively few distinguish cardiac events such as re-infarction,[8,9] although a recent Swedish study reports a 1.2% prevalence of non-fatal AMI at 12 months in MINOCA.[10]

Accordingly, the current study compared outcomes of patients with MINOCA to those with MICAD in relation to: (i) major adverse cardiac events (MACE) over 12 months; and (ii) the components of MACE [all-cause mortality, re-hospitalization for AMI, heart failure (HF), or stroke] over 12 months.

Methods

This study used data from the National Cardiovascular Data Registry (NCDR®) CathPCI Registry linked with corresponding claims data from Centers for Medicare and Medicaid Services (CMS).

Data sources

CathPCI Registry

The NCDR CathPCI Registry is a national quality improvement data registry of the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions. The details and design of the NCDR CathPCI Registry have been previously described.[11] In brief, the CathPCI Registry includes over 1500 facilities enrolled in the USA, with data collected for patients undergoing cardiac catheterization and/or percutaneous coronary intervention (PCI) by trained personnel at each participating institution using a standardized case report form.[12] For this study, the angiography findings and the AMI diagnosis were sourced from the CathPCI Registry version 4.0. The Human Investigation Committee at Yale University School approved the use of a limited data set from the CathPCI registry, which did not require informed consent.

Centers for Medicare and Medicaid *administrative (claims and beneficiary) data*

The CMS database is an administrative claims dataset which contains information on all hospitalizations of patients enrolled in fee-for-service Medicare (the primary health insurance programme for people aged ≥65 years) and includes service dates and ICD-9-CM diagnosis codes. The Medicare inpatient claims file data contains anonymous patient identifiers, which enables follow-up of beneficiaries over time. In addition, the Medicare denominator data, which links to the inpatient data, contains information on beneficiary eligibility, demographic characteristics, and date of death. For this study, the ICD-9-CM primary and secondary diagnosis codes, and date of death were sourced, and the beneficiary ID, admission date and discharge date of the claims were used for linkage to the CathPCI Registry data.

Patient selection and acute myocardial infarction definition

The study cohort included patient admissions in the CathPCI registry between 1 July 2009 and 31 December 2013, who were aged at least 65 years and older to enable linkage to CMS. CathPCI stays where the CAD presentation in the first visit during the stay was either ST-elevation AMI or non-ST-elevation AMI were identified. Subsequently, the patient, discharge diagnosis of AMI, and discharge date in the CathPCI stay were matched to the CMS claims data. CathPCI stays were excluded if they had incomplete data for the estimates of coronary artery stenosis, if patients presented with cardiac arrest within 24 hours of catheterization, if thrombolytics were administered prior to catheterization, and if visits reported AMI as an intra and/or post-procedure complication. The final study sample consisted of CathPCI patients undergoing angiography for AMI with a confirmed AMI discharge diagnosis in the CMS claims data (N = 286 780 total; 276 522 unique patients) (*Figure 1*).

The MINOCA admissions were identified as admissions in which patients did not have evidence of obstructive CAD, defined as no stenosis or stenosis <50% and no history of previous revascularization, and admissions with MICAD were defined as admissions in which the patient stenosis ≥50% in any coronary artery or grafts or with previous or current revascularization,[4,13] based on the estimates of coronary anatomy available in the CathPCI data. Detailed information on the cardiovascular risk profile and discharge medications was not available in CathPCI as this data were more robustly collected for patients undergoing PCI. Therefore, patient risk factors and cardiovascular/comorbid conditions for the CathPCI stays were derived using the claims data from the linked CMS files (defined according to the ICD-9-CM coding).[14–16]

Endpoints

The primary endpoint was MACE at 12 months (defined as the first occurrence of an event in the 12-month time period). Secondary endpoints included the components of MACE over 1-, 6-, and 12 months. The mortality outcomes were derived using the CMS data. Re-hospitalizations post-discharge were defined using the CMS inpatient claim file, identified through the primary diagnosis of ICD-9-CM diagnosis codes (Supplementary material online, *Table S1*).[17–20]

Data linkage and consolidation

The CathPCI patient stays were linked to records in the CMS inpatient claims data using direct patient identifiers that were present in the both the CMS claims files and the CathPCI Registry.[21] To ensure the accuracy of inclusion of true admissions with MINOCA and MICAD patients, CathPCI patient stays included in the study sample required verification of the AMI diagnosis. This was confirmed if the linked CMS record for the CathPCI hospitalization also included AMI as the primary diagnosis (410.X). Matching to the CMS data also allowed: (i) the identification of subsequent inpatient claims for 12 months following discharge for the angiogram; (ii) mortality for any reason (both in-hospital/out of hospital); and (iii) prior inpatient and outpatient claims for 12 months prior to angiography. With the prior inpatient or outpatient claims, we derived the

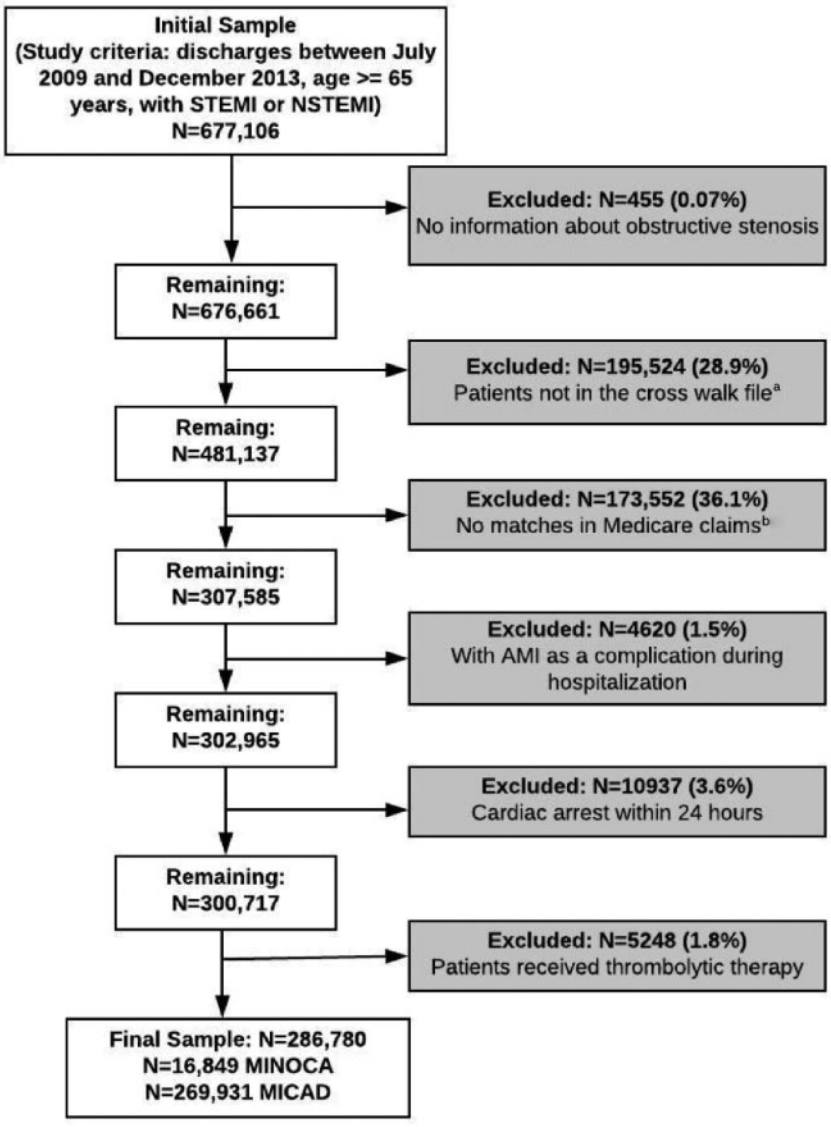


Figure 1 Study sample selection flow diagram. [a]Matching by patients through the National Cardiovascular Data Registry patient ID and Centers for Medicare and Medicaid beneficiary ID in the crosswalk data file. This crosswalk data file was created using the patients' direct identifiers, while the administrative data was requested for all the patients in all the ACC registries. [b]Matching by patient beneficiary ID and the discharge date.

patients' risk factors for adjustment. For post-inpatient claims, we used ICD-9 codes to identify re-hospitalization for AMI, HF, and stroke.

Statistical analysis

Baseline characteristics were examined for the total sample and compared between admissions with MINOCA and MICAD patients using χ^2 tests for categorical variables and *t*-tests for continuous variables. The unadjusted MACE outcomes over 12 months between admissions with MINOCA and admissions with MICAD patients were also compared using χ^2 tests for categorical variables. The cumulative incidence rates for the MACE outcomes over 12 months were calculated for admissions with MINOCA and MICAD and presented as Kaplan–Meir curves.

The MACE outcomes over 1, 6, and 12 months and the components of MACE were examined using Cox proportional-hazard models with competing risks, and sequential adjustment for potential confounders, represented by risk-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). We used this approach to assess the independent effect of MINOCA on outcomes following AMI. More specifically, to examine whether differences in these outcomes persisted after adjustment for demographics, risk factors, and comorbidities and to identify which patient and/or clinical factors may help explain the difference in outcomes. The proportionality assumption was tested and met for the Cox proportional-hazard models used. No violation on the proportional-hazards assumption was found, the proportional-hazards survival models are appropriate for the evaluation of MINOCA on 12-month outcomes. For computing risk analyses, we used the Fine–Gray approach extension of

Table 1 Baseline clinical characteristics stratified by MINOCA and MICAD patients

Characteristics	Total sample (*N* = 286 780)		MINOCA (*N* = 16 849; 5.9%)		MICAD (*N* = 269 931; 94.1%)	
	n	%	*n*	%	*n*	%
Sociodemographics						
Age (years): Mean, SD	75.6	7.3	75.1	6.9	75.6	7.3
Female sex	124 900	43.6	12 970	77.0	111 930	41.5
Race						
White	259 343	90.4	14 637	86.9	244 706	90.7
Black	19 041	6.6	1713	10.2	17 328	6.4
Other	8396	2.9	499	3.0	7897	2.9
Cardiovascular history						
Congestive heart failure	31 571	11.0	1568	9.3	30 003	11.1
Angina pectoris/old myocardial infarction	47 040	16.4	1315	7.8	45 725	16.9
Valvular/rheumatic heart disease	47 232	16.5	3301	19.6	43 931	16.3
Arrhythmias	30 464	10.6	1817	10.8[a]	28 647	10.6
Acute coronary syndrome	25 586	8.9	468	2.7	25 118	9.3
Anterior myocardial infarction	52 139	18.1	2649	15.7	49 490	18.3
Admission presentation						
ST-elevation myocardial infarction	77 305	27.0	2344	13.9	74 961	27.8
Comorbidities						
Cerebrovascular disease	12 099	4.2	529	3.1	11 570	4.3
Stroke	3438	1.2	207	1.2[a]	3231	1.2
Vascular or circulatory disease	26 559	9.3	1168	6.9	25 391	9.4
Diabetes/diabetes complications	106 623	37.2	4352	25.8	102 271	37.9
Renal failure	30 558	10.7	1289	7.7	29 269	10.8
Chronic obstructive pulmonary disease	60 092	21.0	4170	24.8	55 922	20.7
Pneumonia	29 455	10.3	2086	12.4	27 369	10.1
Asthma	8993	3.1	899	5.3	8094	3.0
Drug/alcohol abuse/dependence/psychosis	38 478	13.4	1751	10.4	36 727	13.6
Major psychiatric disorders	6086	2.1	541	3.2	5545	2.1

[a]Denotes non-significant values >0.001.

the Cox regression that models the hazards of the cumulative incidence function.[22,23] Variables included in the model correspond to those in the CMS AMI risk-standardized readmission measure.[15,24] For all outcomes, the first model included sociodemographics (age, sex, and race), the second model included Model 1 and cardiovascular history and risk factors, and the third model included Model 2 and comorbidities (refer to Supplementary material online, *Table S2*). For all statistical analyses, the significance level was two-sided with a *P* value of <0.001. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and version 4.0 of the CathPCI Registry.

Results

Baseline characteristics

Between 1 July 2009 and 31 December 2013, there were 677 106 AMI admissions in CathPCI for patients aged ≥65 years. *Figure 1* outlines the inclusion and exclusions for the study cohort. The final study cohort consisted of 286 780 AMI admissions. Of these, 124 900 (43.6%) were female, the mean age was 75.6 years and 259 343 (90.4%) were white. MINOCA was classified in 16 849 (5.9%) visits (*Table 1*).

Compared to the MICAD patients, MINOCA patients were slightly younger, more likely to be female (77.0% vs. 41.5%; $P < 0.001$), and were more likely to be black (10.2% vs. 6.4%; $P < 0.001$). Patients with MINOCA were less likely to have a history of prior AMI/acute coronary syndrome, or HF, compared with MICAD patients (*Table 1*).

Unadjusted mortality and re-hospitalization outcomes over 12 months

Patients with MINOCA experienced fewer MACE events during the index hospitalization and at 1-, 6-, or 12-month follow-up, compared to those with MICAD (*Table 2*; *Figure 2A–F*). Similarly, all-cause mortality was lower in the MINOCA patients at the index hospitalization and at 1-, 6-, and 12-month follow-up. Overall, re-hospitalization rates were slightly lower over the 12-month follow-up period in

Table 2 Unadjusted mortality and re-hospitalization rates over 12 months stratified by MINOCA and MICAD

Characteristics	Total sample (*N* = 286 780)		MINOCA (*N* = 16 849; 5.9%)		MICAD (*N* = 269 931; 94.1%)	
	n	%	*n*	%	*n*	%
In-hospital mortality	11 322	4.0	348	2.1	10 974	4.1
1-Month outcomes						
MACE (mortality, AMI, HF, stroke)	30 773	10.7	1094	6.5	29 679	11.0
Mortality from discharge	19 313	6.7	735	4.4	18 578	6.9
Re-hospitalization for AMI	3572	1.2	44	0.3	3528	1.3
Re-hospitalization for HF	8368	2.9	289	1.7	8079	3.0
Re-hospitalization for Stroke	932	0.3	64	0.4[a]	868	0.3
Re-hospitalization	41 912	14.6	2135	12.7	39 777	14.7
6-Month outcomes						
MACE (mortality, AMI, HF, stroke)	60 054	20.9	2322	13.8	57 732	21.4
Mortality from discharge	35 004	12.2	1524	9.0	33 480	12.4
Re-hospitalization for AMI	11 361	4.0	134	0.8	11 227	4.2
Re-hospitalization for HF	19 863	6.9	735	4.4	19 128	7.1
Re-hospitalization for Stroke	2646	0.9	179	1.1[a]	2467	0.9
Re-hospitalization	91 500	31.9	4889	29.0	86 611	32.1
12-Month outcomes						
MACE (mortality, AMI, HF, stroke)	27.0	3145	18.7	74 409	27.6	27.0
Mortality from discharge	16.4	2080	12.3	44 958	16.7	16.4
Re-hospitalization for AMI	5.8	221	1.3	16 323	6.0	5.8
Re-hospitalization for HF	9.1	1002	5.9	25 029	9.3	9.1
Re-hospitalization for Stroke	1.4	267	1.6	3887[a]	1.4	1.4
Re-hospitalization	40.9	6443	38.2	110 817	41.1	40.9

AMI, acute myocardial infarction; CAD, coronary artery disease; HF, heart failure; MACE, major adverse cardiac events.
[a]Denotes non-significant values >0.001.

patients with MINOCA compared with MICAD patients (38.2% vs. 41.1% $P < 0.001$), with MINOCA patients having fewer re-hospitalizations for AMI or HF, but a similar rate for stroke.

Independent effect of MINOCA on 12-month outcomes

Figure 3A–B shows the association and/or effect of MINOCA on outcomes at 12 months, sequentially adjusted for confounders. Supplementary material online, *Figures S1A–S2B* show the association and/or effect of MINOCA on outcomes over 1- and 6-month post-AMI.

In the unadjusted model, MINOCA patients had a lower likelihood of MACE (HR = 0.64, 95% CI 0.62–0.66), mortality from discharge (HR = 0.72; 95% CI 0.69–0.76), as well as re-hospitalization (HR = 0.90; 95% CI 0.88–0.93), in comparison to MICAD patients over 12 months. After adjusting for sociodemographics, cardiovascular history, and comorbidities MINOCA patients had a significant but persistently lower hazard of MACE (HR = 0.57, 95% CI 0.55–0.59), mortality following discharge (HR = 0.60, 95% CI 0.57–0.63), and a lower likelihood of re-hospitalization (HR = 0.89; 95% CI 0.86–0.91).

Discussion

To our knowledge, this study represents the largest cohort of MINOCA patients with longitudinal follow-up for adverse events. Moreover, it provides comparable data on outcomes from a MICAD cohort. In this elderly US AMI population, we demonstrate that MINOCA accounts for ~6% of all AMI presentations. Although MACE events over 12 months were lower in patients with MINOCA compared with MICAD, the prognosis amongst MINOCA patients remains of concern. For example, ~5% of MINOCA patients do not survive the first 30 days post-AMI, almost 40% are re-hospitalized within 12 months and the rate of stroke is the same to the rate observed in MICAD patients. Accordingly, the findings of this study underscore the need to closely consider the on-going management of patients with MINOCA. In particular, these patients warrant further investigation to elucidate the underlying aetiology responsible for their AMI, thereby initiating appropriate mechanistic-targeted therapy to prevent future adverse events.

Prevalence of MINOCA

There is increasing awareness that a proportion of AMI patients do not have evidence of obstructive CAD on angiography;

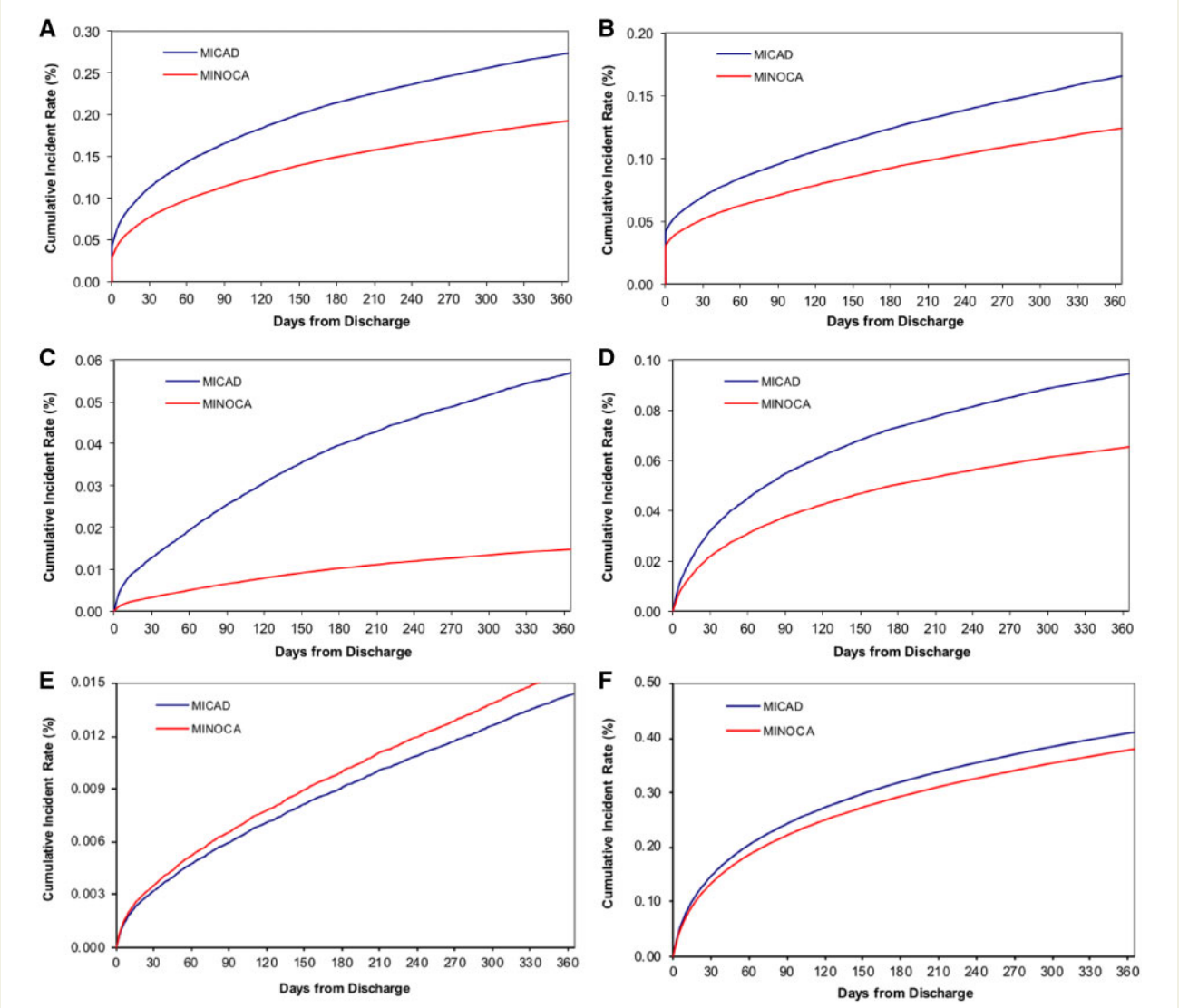


Figure 2 Kaplan–Meier curves for unadjusted incidence of outcomes over 12 months showing the cumulative incidence for (*A*) major adverse cardiac events, (*B*) mortality, (*C*) acute myocardial infarction re-hospitalization, (*D*) heart failure re-hospitalization, (*E*) stroke re-hospitalization, and (*F*) all-cause re-hospitalization (blue line: MICAD; red line: MINOCA).

however, the reported prevalence of these patients has varied due to diverse data collection methods and definitions.[25] A recent systematic review of the published literature using the conventional <50% stenosis[13] threshold for non-obstructive CAD, estimated a prevalence of 6%.[4] More contemporary registry data of unselected AMI patients reveals a prevalence of MINOCA as high as 11%,[26] possibly reflecting the more widespread use of coronary angiography in acute coronary syndromes. The lower prevalence of MINOCA in the present study may have been influenced by the elderly cohort evaluated (mean age 75 years) since the condition is more prevalent in the young.

Previous studies have consistently demonstrated an over-representation of women in the MINOCA cohort compared to those with MICAD.[4] In these studies, which include women of all ages (median age of 55 years), 40% of the MINOCA cohort were women. The VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, which was restricted to AMI patients <55 years, showed that women had five times higher odds of having MINOCA than men.[27] In the present study, where the age is restricted to those above 65 years, this sex difference is also exaggerated with almost 80% of the MINOCA cohort being female. The mechanism responsible for this striking sex difference in elderly MINOCA patients requires further investigation but may include plaque-related events, loss of endogenous oestrogen and/or progestins, the use of hormone replacement therapy or microvascular dysfunction and/or vasospasm.[28–30] Regarding the latter, studies such from WISE (Women's ischaemia Syndrome Evaluation study) have demonstrated that microvascular dysfunction is central to the mechanism of non-obstructive coronary disease in women and accounts for their symptoms and prognosis.[31]

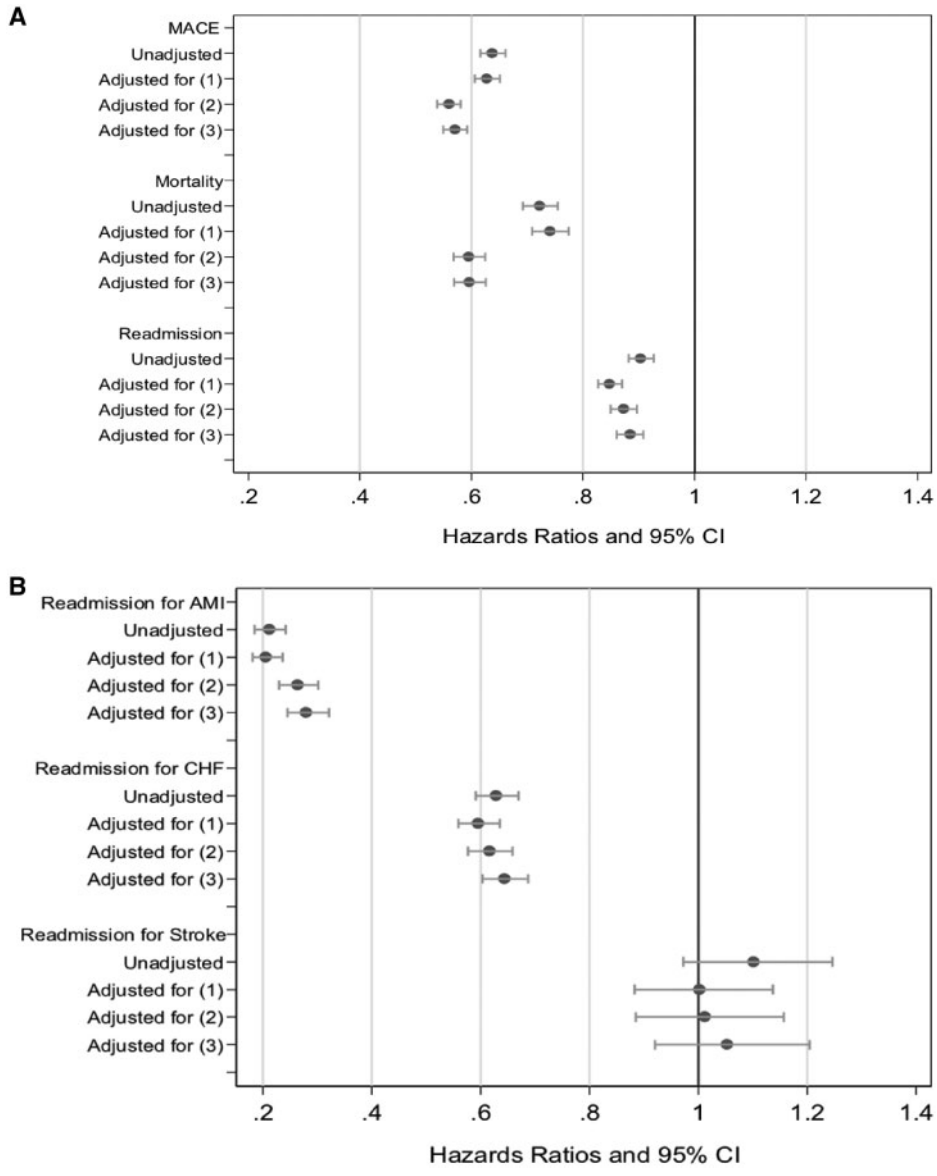
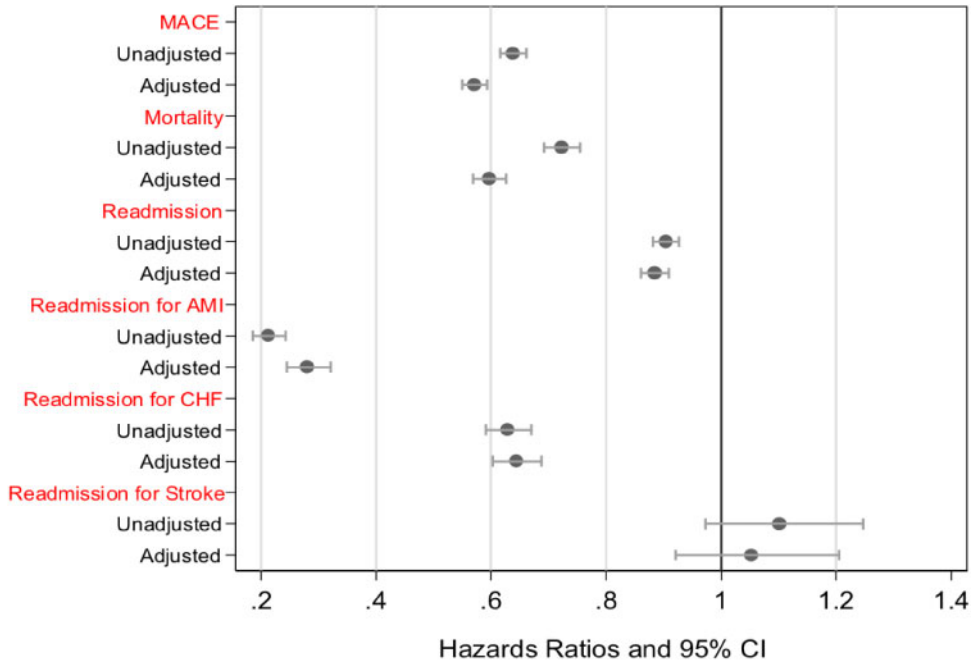


Figure 3 A forest plot showing unadjusted/adjusted hazard ratio and 95% confidence interval for the independent effect of MINOCA on (*A*) 12-month major adverse cardiac events, mortality, and readmission; and (*B*) readmission for acute myocardial infarction, congestive heart failure, and stroke. Cox models, censored at 12 months; competing risk also considered here.

Previous prognostic studies

The prognosis of MINOCA is often presumed to be benign given the absence of obstructive CAD; however, the present study demonstrates a guarded prognosis in relation to all-cause mortality and MACE albeit better than patients with MICAD. The largest study to date exploring in-hospital MACE in MINOCA demonstrated a lower prevalence of events compared to MICAD,[32] however, the AMI population was predominately young and supports a guarded prognosis in MINOCA.

Concerning all-cause mortality at 12 months, this was found to be 12.3% in the present study and although lower than patients with MICAD (16.7%), it is considerably higher than reported from a prior meta-analysis (4.7%)[4] and a recent French registry (3.3%).[33] This may reflect the elderly cohort studied in the present study. Of importance, a prospectively conducted Korean AMI Registry demonstrated that patients with MINOCA had the equivalent 12-month all-cause mortality to those with an AMI with single- or double-vessel CAD.[9] In the present study, a *post hoc* subgroup analysis revealed that, compared to MICAD patients with single- or double-vessel CAD, MINOCA patients had a similar, although statistically lower, 6-month mortality (9.1% vs. 10.1%, $P < 0.001$) and 12-month mortality (12.3% vs. 13.9%, $P < 0.001$). In relation to MACE over the 12-month study period, MINOCA patients had a 43% lower risk as compared with MICAD. The 1.3% re-infarction rate at 12 months amongst



Take home figure A forest plot showing unadjusted/adjusted hazard ratio and 95% confidence interval for the independent effect of MINOCA on 12-month outcomes. In the unadjusted model, MINOCA patients had a lower likelihood of major adverse cardiac events, mortality from discharge, and re-hospitalization vs. MICAD patients. After adjusting for confounders, MINOCA patients had a significant but persistently lower hazard of major adverse cardiac events, mortality following discharge, and a lower likelihood of re-hospitalization.

MINOCA patients observed in this study is consistent with a previous report of 1.4%.[34] Overall, MINOCA patients had lower event rates compared to MICAD patients for all outcomes except for stroke, consistent with a recent report from the national Swedish registry.[10] Of note, the prevalence of hypertension and arrhythmias was similar between MINOCA and MICAD patients which may account for the similar stroke events. Despite a better prognosis compared to MICAD, MINOCA patients still have a higher risk of mortality and recurrent AMI in comparison to a healthy, age and gender matched population, as recently described by a national New Zealand study (11.1% vs. 3.0% at 2 years).[35] This study did not include a control population, however life expectancy at age 65 is 19 years in the USA,[36] but 12% of MINOCA patients were deceased at 1 year, suggesting a higher mortality burden in these patients. Further, MINOCA patients with angiographically smooth coronaries still suffer adverse outcomes with 12-month mortality/recurrent AMI reported to be 3.9%, as compared to 6.1% for MINOCA patients with non-obstructive CAD.[37]

The guarded prognosis in patients with MINOCA beckons the question as to the responsible mechanism. Previous studies have implicated coronary plaque disruption, coronary thrombosis and embolism, epicardial coronary artery spasm, and microvascular dysfunction, as pathophysiological mechanisms.[38,39] In addition, psychosocial factors may also play an important role, such as depression, due to the increased risk of ongoing symptoms in patients without obstructive CAD,[40] and perceived stress, which is associated with increased long-term mortality in AMI patients.[41] Lastly, the differential treatment patterns with cardioprotective medications in patients with MINOCA vs. MICAD is a potential responsible mechanism for their poorer outcomes. This study did not formally evaluate medical management at discharge, however, guideline-recommended therapies are less likely to be prescribed in MINOCA patients,[42] and thus, the role of these therapies in influencing outcomes requires further scrutiny.

Study implications

The guarded prognosis evident in this large study has important implications in the management of patients with MINOCA. First, these patients have a clinically important condition associated with significant morbidity and mortality, and should not be dismissed as having 'minor disease'. Second, the diagnosis of MINOCA should prompt a comprehensive diagnostic work-up to identify the underlying cause of the presentation in each individual patient.[43] This is crucial, as although no randomized trials exist to define the optimal management of these patients, the diagnostic workup can aid in identifying the appropriate forms of targeted therapy, since therapies that may be appropriate for one cause, e.g. anticoagulation for thromboembolism or calcium channel blockers for vasospasm, will not be appropriate for all MINOCA patients. Further, prognosis may vary according to the underlying cause[43] and this should be explored in future multicentre studies that incorporate data on additional diagnostic investigations following angiography. Third, strategies are needed to improve prognosis, and reduce the re-hospitalization burden.

A recent observational study suggests that statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have long-term beneficial effects on MACE in patients with MINOCA.[44] However, this study also demonstrated that dual antiplatelet therapy had no impact on MACE in patients with MINOCA. Hence it cannot be assumed that evidence-based cardioprotective therapies for MICAD are equally effective in MINOCA and dedicated clinical trials establishing their efficacy are required. Lastly, angina burden in AMI patients without obstructive CAD may be as high as those with MICAD,[45] however, patient-reported outcomes measuring psychosocial factors and health status in MINOCA patients have received limited attention, but should be a focus in future prospective studies assessing treatment and prognosis.

Limitations

Our study has several limitations. First, the CathPCI registry accounts for only in-hospital post-angiogram events and therefore the database was linked to CMS claims data to obtain clinical outcomes over 12 months. Although CMS provides a comprehensive data source, this database has inherent limitations including lack of data on AMI patients <65 years and the potential for a billing coding bias associated with administrative claims datasets. In addition, more than 50% of patients in the initial sample were excluded from the study due to completeness or accuracy of the patients' identification data (29%) and the data linkage (25% which may due to the non-Medicare insurance), which may limit the generalizability of our findings. Second, we did not have data on cause-specific mortality or outcomes from a population matched control group, and clinically relevant information which may have influenced outcomes including complete discharge medications and extent of necrosis. The CathPCI dataset routinely captures this information only for PCI patients and thus limits our findings. The CathPCI angiographic interpretation was dependent upon the clinician's angiographic report and thus may be limited in accuracy. Lastly, diagnosis of MINOCA was based upon a discharge diagnosis of AMI. Accordingly, conditions mimicking AMI were clinically excluded (e.g. myocarditis) but whether investigations to actively exclude these non-ischaemic causes (e.g. cardiac magnetic resonance imaging) were undertaken is unknown. Hence it is possible that not all the patients in the study cohort experienced an ischaemic AMI. This equally applies for the MICAD cohort.

Conclusion

In conclusion, although elderly patients with MINOCA have fewer MACE events 12 months after AMI compared to those with MICAD, one in five MINOCA patients will require a cardiovascular-related re-hospitalization and one in ten will not survive by 12 months. Whether conventional cardioprotective therapies shown to improve prognosis in MICAD are also effective in MINOCA necessitates clinical trials specifically targeting this unique condition.

Supplementary material

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

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