Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)

Nathaniel R. Smilowitz, MD; Asha M. Mahajan, MD; Matthew T. Roe, MD, MHS; Anne S. Hellkamp, MS; Karen Chiswell, PhD; Martha Gulati, MD, MS; Harmony R. Reynolds, MD

Background—Sex differences in early mortality after myocardial infarction (MI) vary by age. MI with nonobstructive coronary arteries (MINOCA [<50% stenosis]) is more common among younger patients and women, and MINOCA has a better prognosis than MI with obstructive coronary artery disease (MI-CAD). The relationship between age, sex, and obstructive CAD status and outcomes post-MI has not been established.

Methods and Results—Adults who underwent coronary angiography for acute ST-segment–elevation and non–ST-segment–elevation MI in the National Cardiovascular Data Registry ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines) from 2007 to 2014 were identified. Patients with cardiac arrest, thrombolytic therapy, prior revascularization, or missing demographic or angiographic data were excluded. The primary outcome was all-cause, in-hospital mortality. Secondary outcomes included major adverse cardiovascular events. Demographics, clinical history, presentation, and in-hospital treatments were compared by sex and CAD status (MI-CAD or MINOCA). Mortality and major adverse cardiovascular outcomes were analyzed by age, sex, and CAD status. Among 322 523 patients with MI, MINOCA occurred in 18 918 (5.9%). MINOCA was more common in women than men (10.5% versus 3.4%; $P<0.0001$), and women had higher mortality than men overall (3.6% versus 2.4%; $P<0.0001$). In-hospital mortality was lower after MINOCA than MI-CAD (1.1% versus 2.9%; $P<0.0001$). Among patients with MI-CAD, women had higher mortality than men (3.9% versus 2.4%; $P<0.0001$) while no sex difference in mortality was observed with MINOCA (1.1% versus 1.0%; $P=0.84$). The higher risk of post-MI death among women with MI-CAD was most pronounced at younger ages.

Conclusions—MINOCA was associated with lower mortality than MI-CAD. Higher risk of post-MI death among women in comparison to men was restricted to patients with MI-CAD. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003443. DOI: 10.1161/CIRCOUTCOMES.116.003443.)**

Key Words: acute coronary syndrome ■ mortality ■ myocardial infarction ■ sex ■ women ■ nonobstructive

Acute myocardial infarction (MI) occurs in >750 000 patients in the United States each year and may occur with or without obstructive coronary artery disease (CAD) at angiography.[1] The phenomenon of MI with nonobstructive CAD (MINOCA), defined by <50% stenosis of all major epicardial vessels, occurs in ≈6% of acute MI and is more common among younger patients and women.[2,3] Young women presenting with MI present an epidemiological paradox: although they have higher in-hospital mortality than their male counterparts of similar age,[4] young women are less likely to have obstructive CAD at angiography with MI,[5–9] and patients with MINOCA have a better prognosis than MI with obstructive CAD (MI-CAD).[8,10,11] However, it is not known whether the excess risk of post-MI death among younger women is most pronounced among those with MI-CAD.[4] Evidence from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of American College of Cardiology/American Heart Association Guidelines registry of non–ST-segment–elevation MI (NSTEMI) suggests that outcomes are similar between men and women with MINOCA, but interactions between age, sex, obstructive CAD status, and post-MI outcomes have not been systematically evaluated.[8] Furthermore, because MINOCA represents a minority of acute MI, prior studies have not been sufficiently large to determine predictors of adverse outcomes in this population. We analyzed patients enrolled in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines) to determine the clinical characteristics,

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From the Cardiovascular Clinical Research Center, Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY (N.R.S., H.R.R.); Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY (A.M.M.); Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (M.T.R., A.S.H., K.C.); and Division of Cardiology, Department of Medicine, University of Arizona-Phoenix (M.G.).

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Correspondence to Harmony R. Reynolds, MD, Cardiovascular Clinical Research Center, 530 First Ave SKI-9R, New York, NY 10016. E-mail Harmony.Reynolds@NYUMC.org

WHAT IS KNOWN

- Myocardial infarction (MI) with nonobstructive coronary arteries is more common among women and younger patients, and MI with nonobstructive coronary arteries has a better prognosis than MI with obstructive coronary artery disease.

WHAT THE STUDY ADDS

- In a large multicenter registry of 322 523 patients with MI, MI with nonobstructive coronary arteries occurred in 5.9% of cases and was more common among women, younger individuals, and black patients.
- Among patients with MI with obstructive coronary artery disease, women had higher in-hospital mortality than men, a finding that was most pronounced at younger ages.
- No sex difference in mortality was observed with MI with nonobstructive coronary arteries.

treatment, predictors of in-hospital mortality, and clinical outcomes of patients by age, sex, and obstructive CAD status.

Methods

Data were obtained from the National Cardiovascular Data Registry ACTION Registry-GWTG, a national, outcomes-based cardiovascular quality improvement registry sponsored by the American College of Cardiology and the American Heart Association. The registry collects retrospective inpatient data on consecutive patients with MI at >750 participating hospitals in the United States. Standardized data elements, including demographics, clinical characteristics, and in-hospital treatments, and outcomes are captured electronically and submitted into a secure, centralized database. The design and conduct of this registry have been previously described.[12] Waiver of written informed consent and authorization for this study was granted by Chesapeake Research Review Incorporated. The Duke Clinical Research Institute served as the data coordinating center and analyzed deidentified patient data.

Patients in the ACTION Registry-GWTG who underwent coronary angiography for ST-segment–elevation MI (STEMI) or NSTEMI at 765 clinical sites between January 1, 2007, and December 31, 2014, were included in this analysis. From the total population of 596 820 patients with STEMI and NSTEMI, those presenting with cardiac arrest (n=9999), recent cocaine use (n=3632), STEMI with thrombolytic therapy before catheterization (n=12 076), prior coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting (n=186 829), without angiographic data (n=61 218), or missing age or sex data (n=543) were excluded. The remaining 322 523 patients (54.0%) were included in the final analysis.

Obstructive CAD at angiography (MI-CAD) was defined as ≥50% stenosis in any major coronary vessel; MINOCA was defined as <50% stenosis in all major epicardial coronary vessels. Baseline demographics, clinical characteristics, in-hospital and discharge medications, and in-hospital clinical outcomes were compared by age, sex, and CAD status at the time of MI (MI-CAD versus MINOCA). The primary outcome was in-hospital all-cause mortality. A hypothesis-generating, exploratory analysis examined a composite of major adverse in-hospital cardiovascular events (MACE) consisting of in-hospital death, reinfarction, cardiogenic shock, or heart failure and its individual nonfatal components.

Statistical Analysis

Patient demographics, medical history, clinical presentation, laboratory results, and in-hospital treatments were compared between patients by sex within CAD status (MI-CAD or MINOCA) groups and by CAD status within sex. Continuous variables are reported as median (25th, 75th percentile) and were compared with Wilcoxon rank-sum tests. Categorical variables were compared with Pearson χ^2 tests.

To summarize in-hospital mortality among subgroups by age, age was categorized as <50 years, ≥80 years, and by decade from 50 to 79. Among specific subgroups of interest, event rates were compared with Pearson χ^2 tests. In addition, a logistic regression model was developed including age as a continuous variable, sex, CAD status, and all 2-way interaction terms between these variables. Odds ratios (ORs) derived from this model were not adjusted for other cardiovascular risk factors. Initially, a 3-way interaction term for age×sex×CAD status was included; it was not significant (P=0.70) and was removed from the model for all subsequent steps. It has previously been determined that age has a linear relationship with the log-odds of in-hospital mortality in ACTION, and therefore age was fit as a straight line in the logistic model. When estimates across age groups were required, we selected the midpoint of each group by decade (ie, 55, 65, 75), with 45 for the youngest group and 85 for the oldest group. ORs generated from the model were used to plot the risk of mortality in age groups by decade, sex, and CAD status. To illustrate the results of the model in younger patients, ORs for patients 45 years of age were calculated from the model for MI-CAD versus MINOCA among women and for women versus men within CAD status groups. An age of 45 years has been selected to define younger MI cohorts in prior analyses of the ACTION Registry-GWTG data.[13]

Independent predictors of in-hospital mortality that had significant interactions with sex and CAD status were identified using an established ACTION Registry-GWTG mortality adjustment model.[14] A 4-level variable comprising the 4 sex and CAD status combinations was used. Interactions between predictors of mortality and this variable were determined using forward stepwise selection. The final model included the 4-level subgroup variable, all standard predictors, and all interactions with P<0.05. For predictors with significant interactions, ORs with 95% confidence intervals are presented within the sex/CAD status subgroups. All comparisons were 2 tailed, and a P<0.05 was considered statistically significant for all tests. Statistical analysis was performed with SAS version 9.2 or higher (SAS Institute, Cary, NC).

Results

Among 322 523 patients with STEMI or NSTEMI who met study inclusion criteria, 18 918 (5.9%) had MINOCA. MINOCA was more common in women than men (10.5% versus 3.4%; P<0.0001) and in patients presenting with NSTEMI than STEMI (8.9% versus 2.2%; P<0.0001). Women were more likely than men to have MINOCA whether they presented with STEMI (3.6% versus 1.6%, respectively; P<0.0001) or NSTEMI (15.0% versus 5.1%; P<0.0001). Among patients excluded for missing age or sex data, ≈70% had angiographic data, and of these, 3.4% had MINOCA.

Characteristics of the study population are displayed in Table 1. Patients with MINOCA were younger than those with MI-CAD in both sexes. Men with MI were younger than women with MI for both MINOCA and MI-CAD (59 versus 66 years, P<0.0001 for MI-CAD; 54 versus 63 years, P<0.0001 for MINOCA). The likelihood of MINOCA varied by race; patients of both sexes with MINOCA were more likely to be individuals of black race than patients with MI-CAD (23% versus 9% for men; 16% versus 13% for women; P<0.0001). Patients with MINOCA had fewer traditional risk factors for coronary heart disease, including dyslipidemia, diabetes mellitus, and tobacco use, in comparison to patients with MI-CAD. In contrast, patients with MINOCA were more likely to have end-stage renal disease requiring hemodialysis, prior heart failure, atrial fibrillation or flutter, or chronic lung disease (Table 1).

Table 1. Characteristics of the Study Population

	All Patients	Men			Women		
		MI-CAD	MINOCA		MI-CAD	MINOCA	
	(n=322 523)	(n=202 821)	(n=7 155)	*P* Value*	(n=100 784)	(n=11 763)	*P* Value†
Age, y	61 (52, 71)	59 (51, 69)	54 (44, 64)	<0.0001	66 (56, 77)	63 (53, 74)	<0.0001
<50	18% (57 879)	20% (40 015)	38% (2732)		13% (13 080)	17% (2052)	
50–59	27% (86 744)	30% (61 653)	27% (1942)		20% (20 498)	23% (2651)	
60–69	26% (84 060)	27% (54 654)	19% (1386)		25% (25 051)	25% (2969)	
70–79	18% (56 588)	15% (30 803)	10% (746)		22% (22 513)	22% (2526)	
80–89	12% (37 252)	8% (15 696)	5% (349)		20% (19 642)	13% (1565)	
Race				<0.0001			<0.0001
White	87% (276 661)	88% (176 833)	75% (5305)		85% (84 982)	82% (9541)	
Black	11% (33 566)	9% (17 489)	23% (1621)		13% (12 560)	16% (1896)	
Asian	2% (5821)	2% (4147)	1% (95)		2% (1450)	1% (129)	
American Indian/Alaskan Native	1% (1934)	1% (1203)	1% (40)		1% (608)	1% (83)	
Native Hawaiian/Pacific Islander	<1% (380)	<1% (253)	<1% (9)		<1% (108)	<1% (10)	
Ethnicity							
Hispanic/Latino	5% (16 724)	6% (11 147)	7% (481)	<0.0001	4% (4433)	6% (663)	<0.0001
Medical history							
Hypertension	65% (207 857)	60% (122 436)	59% (4248)	0.091	73% (73 067)	69% (8106)	<0.0001
Dyslipidemia	50% (160 002)	48% (98 152)	40% (2881)	<0.0001	53% (53 402)	47% (5567)	<0.0001
Current or recent smoker (<1 y)	38% (123 414)	41% (82 722)	36% (2576)	<0.0001	35% (35 437)	23% (2679)	<0.0001
Diabetes mellitus	26% (83 471)	24% (47 681)	19% (1336)	<0.0001	32% (31 966)	21% (2488)	<0.0001
Currently on dialysis	1% (4459)	1% (2254)	2% (143)	<0.0001	2% (1894)	1% (168)	0.0005
Prior MI	6% (20 754)	6% (12 199)	7% (496)	0.0013	7% (7130)	8% (929)	0.0011
Prior heart failure	5% (16 463)	4% (7521)	8% (590)	<0.0001	7% (7318)	9% (1034)	<0.0001
Atrial fibrillation or flutter‡	5% (14 061)	4% (7482)	9% (611)	<0.0001	6% (5033)	8% (935)	<0.0001
Chronic lung disease‡	11% (30 613)	9% (15 792)	12% (835)	<0.0001	14% (12 086)	16% (1900)	<0.0001
Prior stroke	5% (16 735)	4% (8769)	5% (353)	0.013	7% (6975)	5% (638)	<0.0001
Peripheral artery disease	5% (17 250)	5% (10 005)	3% (229)	<0.0001	7% (6570)	4% (446)	<0.0001
Cardiac status (on first medical contact)							
Heart rate	80 (68, 95)	80 (67, 94)	84 (71, 100)	<0.0001	82 (70, 97)	85 (72, 101)	<0.0001
Systolic BP	146 (126, 167)	146 (127, 166)	142 (124, 162)	<0.0001	146 (125, 168)	146 (126, 167)	0.20
ECG Findings							
STEMI (or STEMI equivalent)	45% (146 003)	49% (99 441)	22% (1593)	<0.0001	43% (43 358)	14% (1611)	<0.0001
ST elevation	98% (142 417)	98% (97 335)	95% (1517)	<0.0001	97% (42 106)	91% (1459)	<0.0001
LBBB	2% (2549)	1% (1385)	4% (69)	<0.0001	2% (952)	9% (143)	<0.0001
Isolated posterior MI	1% (926)	1% (649)	<1% (7)	0.29	1% (261)	1% (9)	0.82
ST depression	22% (37 762)	23% (23 252)	12% (636)	<0.0001	22% (12 705)	12% (1169)	<0.0001
Transient ST elevation	3% (5044)	3% (3124)	3% (136)	0.015	3% (1582)	2% (202)	<0.0001
T-wave inversion	15% (25 863)	14% (14 334)	12% (665)	<0.0001	16% (9348)	15% (1516)	0.0007

(*Continued*)

Table 1. Continued

	All Patients	Men			Women		
		MI-CAD	MINOCA		MI-CAD	MINOCA	
	(n=322 523)	(n=202 821)	(n=7 155)	*P* Value*	(n=100 784)	(n=11 763)	*P* Value†
Laboratory values (initial unless noted otherwise)							
Initial troponin (×ULN)	2.1 (0.4, 14.6)	2.0 (0.4, 14.5)	2.0 (0.4, 11.4)	0.21	2.4 (0.5, 15.4)	2.5 (0.6, 11.3)	<0.0001
Peak troponin (×ULN)	65.6 (13.7, 308.0)	82.1 (17.0, 380.0)	18.9 (4.4, 83.6)	<0.0001	55.9 (12.2, 253.1)	17.0 (4.8, 60.4)	<0.0001
Total cholesterol, mg/dL	171 (144, 201)	170 (143, 199)	159 (134, 186)	<0.0001	176 (147, 208)	167 (142, 194)	<0.0001
HDL, mg/dL	37 (31, 46)	35 (30, 43)	38 (30, 47)	<0.0001	42 (34, 51)	48 (38, 59)	<0.0001
LDL, mg/dL	103 (79, 129)	103 (80, 129)	93 (72, 117)	<0.0001	104 (79, 132)	93 (72, 117)	<0.0001
Triglycerides, mg/dL	124 (86, 185)	128 (88, 190)	110 (75, 166)	<0.0001	122 (85, 179)	100 (71, 147)	<0.0001
Creatinine, mg/dL	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	0.017	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	<0.0001
Hemoglobin, g/dL	14.3 (13.0, 15.5)	14.9 (13.7, 15.8)	14.7 (13.5, 15.7)	<0.0001	13.3 (12.1, 14.4)	13.3 (12.3, 14.2)	0.12
Hemoglobin A1C, %	6.1 (5.6, 7.3)	6.0 (5.6, 7.1)	5.9 (5.5, 6.7)	<0.0001	6.2 (5.7, 7.6)	5.9 (5.5, 6.7)	<0.0001
BNP, pg/mL	159 (44, 491)	117 (32, 390)	126 (33, 456)	0.037	248 (78, 667)	197 (59, 582)	<0.0001

Continuous variables are shown as median (25th, 75th percentiles) and compared between obstructive and nonobstructive CAD groups (within sex) and between men and women (within MI-CAD or MINOCA groups) using Wilcoxon rank-sum tests. Categorical variables are shown as % (n) and are compared using Pearson χ^2 tests. ACTION-Registry GWTG indicates Acute Coronary Treatment Intervention Outcomes Network Registry-Get With the Guidelines; BP, blood pressure; BNP, B-type natriuretic peptide; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LBBB, left bundle branch block; MI, myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; STEMI, ST-segment–elevation myocardial infarction; and ULN, upper limit of normal.

*P value for comparison of obstructive vs nonobstructive CAD among men.

†P value for comparison of obstructive vs nonobstructive CAD among women.

‡Data captured on version 2 of the ACTION-Registry GWTG data collection form; denominators reflect a subset (88% [n=284 596]) of the total cohort.

At first medical contact, women and men with MINOCA had higher heart rates than those with MI-CAD and were less likely to have ECG abnormalities consistent with STEMI or a STEMI equivalent (17% versus 47%). In both sexes, initial and peak serum troponin levels were lower in patients with MINOCA in comparison to MI-CAD. For both MINOCA and MI-CAD, peak troponin levels were lower in women than men (82.1 versus 55.9 × upper limit of normal, *P*<0.0001 for MI-CAD; 18.9 versus 17.0 × upper limit of normal, *P*=0.0012 for MINOCA). Patients with MINOCA were less likely to receive guideline-directed medical therapy for MI than patients with MI-CAD (Table I in the Data Supplement).

In-Hospital Mortality

In-hospital mortality was lower in patients with MINOCA than MI-CAD (1.1% versus 2.9%; *P*<0.0001). Among patients with MI-CAD, women had higher mortality than men (3.6% versus 2.4%; *P*<0.0001). No sex difference in mortality was observed with patients with MINOCA (1.1% versus 1.0%; *P*=0.84). At all ages, women had greater differential in mortality between MI-CAD and MINOCA compared with men (interaction *P*=0.0008; Figure). The relationship between patient age and mortality varied by sex and also by obstructive CAD status. There was a stronger relationship between older age and mortality in patients with MI-CAD in comparison to MINOCA (interaction *P*<0.0001) and in men versus women (interaction *P*=0.0013). In-hospital mortality rates by age, sex, and CAD status are shown in Table 2.

To understand the previously identified excess mortality risk among young women with MI and the relationship between age, sex, and CAD status, we examined mortality rates in patients aged <60 years. Among these younger patients, MINOCA mortality was lower than for MI-CAD (0.7% versus 1.1%; *P*<0.0001). Women aged <60 years old had higher mortality than similarly aged men (1.3% versus 1.1%; *P*=0.0001) despite a much greater frequency of MINOCA (12.3% versus 4.4%; *P*<0.0001) because of excess mortality among young women with MI-CAD in comparison to their male counterparts (OR, 1.35; 95% confidence interval, 1.22–1.55; *P*<0.0001, estimated for patients 45 years of age). Among women aged <60 years, patients with MI-CAD had ≈2-fold higher odds of mortality in comparison to MINOCA (1.4% versus 0.8%; *P*=0.002; OR, 1.86; 95% confidence interval, 1.37–2.54; *P*<0.0001; estimated for patients 45 years of age).

Predictors of In-Hospital Mortality With Interactions by Sex and CAD Status

Most established predictors of mortality in the ACTION-GWTG registry[14] were similarly predictive among patients with MI-CAD and MINOCA. However, heart failure with shock at presentation and electrocardiographic ST-segment elevation were more strongly associated with in-hospital mortality among patients with MINOCA than MI-CAD (Table 3). In addition, 5 other established predictors of mortality demonstrated a significant interaction with sex and CAD status: weight, heart rate, systolic blood pressure, prior systolic heart failure, and health insurance status. There was no significant interaction between race (white versus non-white) and sex/CAD group.

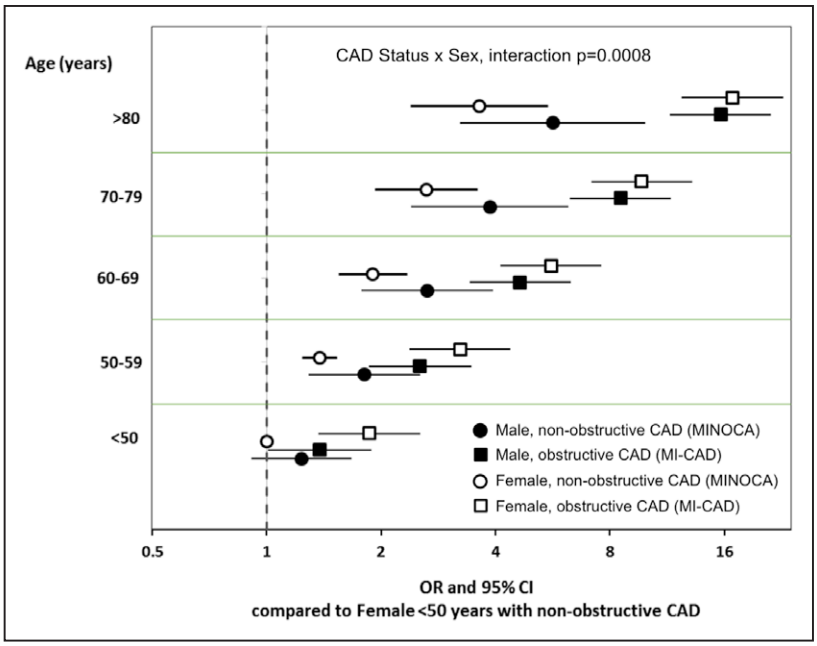

Figure. Interaction between sex, coronary artery disease (CAD) status, and in-hospital mortality. CI indicates confidence interval; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; and OR, odds ratio.

Major Adverse Cardiovascular Events

The composite clinical end point of MACE (in-hospital death, reinfarction, cardiogenic shock, or heart failure) was reported in 9.6% of patients overall. The frequency of MACE was significantly higher in patients with MI-CAD than MINOCA (9.9% versus 4.9%; $P<0.0001$). Women had higher incidence of MACE in comparison to men overall (11.5% versus 8.6%; $P<0.0001$) and in subgroups of MI-CAD (12.3% versus 8.7%; $P<0.0001$) and MINOCA (5.4% versus 4.1%; $P<0.0001$). In all subgroups, the incidence of MACE increased with advancing age (Figure in the Data Supplement).

Table 2. In-Hospital Mortality Rates by Age, Sex, and CAD Type

Age, y	Men	Women
All patients		
<50	0.7% (318/42 747)	1.0% (158/15 132)
50–59	1.3% (799/63 595)	1.5% (336/23 149)
60–69	2.3% (1292/56 040)	2.7% (758/28 020)
70–79	4.1% (1297/31 549)	4.3% (1087/25 039)
≥80	7.7% (1232/16 045)	8.1% (1713/21 207)
All ages	2.4% (4938/209 976)	3.6% (4052/112 547)
Obstructive CAD		
<50	0.8% (303/40 015)	1.1% (147/13 080)
50–59	1.3% (786/61 653)	1.5% (309/20 498)
60–69	2.3% (1269/54 654)	2.9% (735/25 051)
70–79	4.2% (1281/30 803)	4.7% (1056/22 513)
≥80	7.8% (1222/15 696)	8.6% (1682/19 642)
All ages	2.4% (4861/202 821)	3.9% (3929/100 784)
Nonobstructive CAD		
<50	0.5% (15/2732)	0.5% (11/2052)
50–59	0.7% (13/1942)	1.0% (27/2651)
60–69	1.7% (23/1386)	0.8% (23/2969)
70–79	2.1% (16/746)	1.2% (31/2526)
≥80	2.9% (10/349)	2.0% (31/1565)
All ages	1.1% (77/7155)	1.0% (123/11 763)

CAD indicates coronary artery disease.

Discussion

This is the largest study to explore the relationships between age, sex, and obstructive CAD status on in-hospital mortality post-MI. In the large, multicenter ACTION Registry-GWTG, 5.9% of patients undergoing angiography for MI had MINOCA. MINOCA remains a relatively common but incompletely understood clinical entity, associated with major adverse cardiovascular outcomes in-hospital in 5% of patients in this cohort. The likelihood of nonobstructive disease was higher in younger patients with MI, women, and patients of African race, consistent with previously published data.[10,15,16] In-hospital mortality with MINOCA was significantly lower than with MI-CAD. In models evaluating the risk of in-hospital mortality, we identified interactions between sex and obstructive CAD status, age and sex, and age and obstructive CAD status. Although there was no sex difference in early mortality among patients with MINOCA, there was a higher rate of post-MI death among women with MI-CAD in comparison to men, with excess risk associated with female sex and most pronounced at younger ages.

The present analysis illuminates the paradox that young women have higher in-hospital mortality post-MI than their male counterparts[4] yet are also more likely to have MINOCA at angiography, which is a lower-risk MI phenotype.[5–11] Our results confirm that the excess risk of post-MI death in women is restricted to those with MI-CAD and reinforce that women with MI-CAD continue to be a vulnerable group that may benefit from redoubled efforts to improve outcomes.

Although sex differences in outcomes have been consistently reported for MI, absolute rates of in-hospital mortality

Table 3. Predictors of In-Hospital Mortality in the Presence of Interactions With Sex/CAD Type*

	P Value	MINOCA		MI-CAD	
		Women, OR (95% CI)	Men, OR (95% CI)	Women, OR (95% CI)	Men, OR (95% CI)
Demographics					
Weight, kg*	0.009	0.92 (0.82–1.03)	0.87 (0.74–1.02)	1.01 (0.98–1.03)	1.03 (1.01–1.06)
Insurance†	<0.0001				
Medicare		0.83 (0.52–1.33)	0.96 (0.53–1.74)	1.12 (1.04–1.20)	1.18 (1.10–1.27)
Medicaid		4.37 (2.13–8.97)	1.93 (0.71–5.22)	1.33 (1.09–1.62)	1.30 (1.08–1.57)
Other insurance		1.30 (0.27–6.19)	0.59 (0.13–2.73)	1.20 (0.83–1.74)	0.81 (0.65–1.02)
Self-pay		3.63 (1.99–6.64)	1.18 (0.55–2.52)	1.37 (1.18–1.58)	1.74 (1.57–1.92)
Medical history					
History of congestive heart failure	0.004	0.91 (0.50–1.65)	0.55 (0.25–1.22)	1.22 (1.09–1.36)	0.99 (0.88–1.11)
Presentation					
Heart rate	<0.0001				
Below 70 bpm‡		1.10 (0.99–1.22)	0.93 (0.80–1.07)	0.95 (0.93–0.97)	0.98 (0.96–1.00)
Above 70 bpm§		1.03 (0.99–1.07)	1.05 (1.01–1.09)	1.05 (1.04–1.06)	1.08 (1.07–1.09)
Systolic blood pressure‖	<0.0001	1.16 (1.06–1.27)	1.17 (1.05–1.30)	1.16 (1.14–1.18)	1.21 (1.20–1.23)
Heart failure±shock¶	<0.0001				
Heart failure with shock		12.80 (7.14–22.94)	13.79 (7.02–27.09)	7.53 (6.80–8.33)	8.73 (8.03–9.50)
Heart failure only		2.10 (1.25–3.53)	2.52 (1.30–4.91)	1.77 (1.61–1.95)	2.58 (2.36–2.82)
ECG findings#	<0.0001				
ST-segment elevation		5.99 (3.89–9.22)	4.23 (2.43–7.35)	2.57 (2.35–2.80)	2.33 (2.15–2.53)
ST depressions/transient ST elevation		1.68 (0.90–3.15)	1.96 (0.98–3.93)	1.57 (1.40–1.77)	1.43 (1.29–1.60)

Age, race, hypertension, diabetes mellitus, PAD, tobacco use, dyslipidemia, prior MI, prior stroke, hemoglobin, creatinine, troponin, and home cardiovascular medications did not exhibit interactions with sex and obstructive CAD status. CAD indicates coronary artery disease; CI, confidence interval; MI, myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; OR, odds ratio; and PAD, peripheral artery disease.

*OR per 10-kg decrease <105 kg.

†Reference group: Health Maintenance Organization (HMO) insurance status.

‡OR per 5-bpm decrease in heart rate.

§OR per 5-bpm increase in heart rate.

‖OR per 10-mm Hg decrease in systolic blood pressure <140 mm Hg.

¶Reference group: patients without heart failure.

#Reference group: vs T-wave inversions or other ECG findings.

in women and men are lower in the present analysis than in a prior analysis addressing the interaction between age and sex on mortality in the National Registry of Myocardial Infarction from the years 2004 to 2006.[17] That analysis showed a reduction in the excess risk associated with female sex as compared with earlier time periods. This beneficial trend, borne out in the present study as well, may be attributable to increased awareness of MI risk among young women and their physicians, as well as more consistent application of guideline-recommended therapies.[18] Alternatively, increased biomarker sensitivity with the newer generations of the cardiac troponin assay may simply identify greater numbers of lower-risk patients with MI. Regardless, excess risk among young women continues to be apparent in our analysis of data collected in the years 2007 to 2014. Although the underlying cause of this finding is unknown, the excess risk of mortality in young women with MI-CAD may be related to a lack of early detection of and treatment for CAD and cardiovascular risk factors in this population, atypical symptoms of ischemia, and delayed hospital presentations with MI.

The present analysis focuses on in-hospital events documented in the ACTION-GWTG Registry, but adverse clinical outcomes in patients with MINOCA are not exclusively in-hospital or early post-MI. In a systematic review of studies reporting long-term outcomes of MINOCA, all-cause mortality at 12 months was 4.7%.[16] Four-year mortality was 13.4%, and MI recurrence rate was 7.1% in a large registry study of patients with MINOCA.[19] Furthermore, evidence from autopsy studies confirms pathological evidence of fatal MI in the absence of obstructive epicardial coronary disease.[20] Some patients with MINOCA do not survive to medical contact and are consequently not included in reports of patients hospitalized with acute MI.

Despite increasing attention to MINOCA during the past decade, its mechanisms remain uncertain. Some cases are caused by atherosclerotic plaque rupture with myocardial necrosis mediated by embolization of nonocclusive thrombus

and/or superimposed coronary artery spasm.[21,22] Additional mechanisms include dissection or embolism, takotsubo syndrome, and clinically unrecognized myocarditis.[3,23] Clinician uncertainty on the pathogenesis of MINOCA may explain less frequent prescription of antiplatelet therapies, statins, and other conventional secondary prevention measures to these patients. Furthermore, because of mechanistically distinct possible pathogeneses of MINOCA, including those unrelated to coronary atherosclerosis or thrombosis, optimal treatment of MINOCA may differ from conventional guideline-directed medical therapy for MI in some cases. Consequently, regardless of age and sex, patients with MINOCA were less likely to receive guideline-directed medical therapy for MI in-hospital and at discharge than patients with MI-CAD, as previously observed.[6,7,9,24]

This is the first study to identify predictors of in-hospital mortality among patients with MINOCA. Electrocardiographic ST-segment elevation and heart failure with shock at presentation were stronger predictors of in-hospital mortality with MINOCA than MI-CAD. It remains uncertain whether these predictors of mortality may be used to identify MINOCA subgroups with any particular underlying mechanism. Fulminant myocarditis may present clinically as MINOCA with shock, with the true underlying diagnosis recognized only after cardiac magnetic resonance imaging or myocardial biopsy.[25] Increased in-hospital mortality has also been reported for patients with shock and an admission diagnosis of takotsubo syndrome.[26] In that study, the majority of patients with Takotsubo syndrome who died had other critical illness, such as subarachnoid hemorrhage or sepsis. We did not have information about left ventricular dysfunction or associated critical illness in this analysis. Electrocardiographic ST-segment elevation has been observed in MINOCA in the setting of various underlying diagnoses, but no association between electrocardiographic findings and any particular underlying mechanism has been established. Other predictors of mortality that had significant interactions with sex and CAD status in the ACTION Registry-GWTG are of uncertain clinical significance.

Limitations

There are notable limitations of this large, real-world observational registry study of consecutive patients with MI. First, patients who did not undergo angiography were excluded from this analysis, potentially introducing selection bias. We used an established multivariable model to adjust for demographic and clinical covariates, but unmeasured confounders cannot be excluded. The underlying mechanisms of MINOCA, which may vary considerably from patient to patient, could not be established from the data available in this large registry. Detailed findings from intravascular imaging or results of cardiac magnetic resonance imaging were not available for review. Only in-hospital outcomes were available from the ACTION-Registry GWTG. Interactions between discharge medical therapy and adverse cardiovascular events at long-term follow-up could not be explored. These results reflect outcomes from participating National Cardiovascular Data Registry centers in the United States and may not be generalizable to other practices or settings. The nonfatal components of the composite of MACE are based on site report without a rigorous process to ensure complete ascertainment and with no independent adjudication; these events may be under-reported. Still, this large cohort provides novel data on the real-world outcomes of men and women of various ages with MINOCA and MI-CAD.

Conclusions

In a cohort of patients presenting with STEMI or NSTEMI without prior coronary revascularization, MINOCA occurred in 5.9% of cases. Women had a greater risk of post-MI death in comparison to men, a finding that was restricted to patients with MI-CAD and was most pronounced at younger ages. MINOCA was associated with lower mortality than MI-CAD. Even so, MINOCA was associated with a reported 5% rate of in-hospital MACE, and mechanisms of adverse outcomes in patients with MINOCA warrant further study.

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Disclosures

None.

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Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)

Nathaniel R. Smilowitz, Asha M. Mahajan, Matthew T. Roe, Anne S. Hellkamp, Karen Chiswell, Martha Gulati and Harmony R. Reynolds

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Medications administered in-hospital and prescribed at discharge by CAD status.

	MINOCA	MI-CAD	P-value
First 24 hours of hospitalization			
Aspirin	94.3%	96.8%	<0.0001
P2Y12 inhibitor *	36.6%	71.6%	<0.0001
Statin	50.4%	67.1%	<0.0001
ACEi/ARB	38.7%	46.2%	<0.0001
Beta-blocker	72.5%	79.8%	<0.0001
Anticoagulant (any)	85.4%	95.7%	<0.0001
Hospital discharge			
Aspirin	85.3%	96.9%	<0.0001
P2Y12 inhibitor *	27.2%	83.4%	<0.0001
Statin	71.2%	93.3%	<0.0001
ACEi/ARB	57.9%	68.8%	<0.0001
Beta-blocker	77.0%	92.7%	<0.0001

* Clopidogrel, ticlopidine, prasugrel, or ticagrelor
Similar relationships were observed in both sexes (data not shown).

Supplemental Figure: Composite clinical endpoint of major adverse cardiovascular events (in-hospital death, reinfarction, cardiogenic shock, or heart failure) by age group, sex, and CAD status.