Comparison of Patients With Nonobstructive Coronary Artery Disease With Versus Without Myocardial Infarction (from the VA Clinical Assessment Reporting and Tracking [CART] Program)

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Comparisons of the outcomes of patients with myocardial infarction with nonobstructive coronary artery disease (MINOCA) and patients with nonobstructive coronary artery disease (CAD) without myocardial infarction (MI) are limited. Here we compare the outcomes of patients with MINOCA and patients with nonobstructive CAD without MI and assess the influence of medical therapy on outcomes in these patients. Veterans who underwent coronary angiography between 2008 to 2017 with nonobstructive CAD were divided into those with or without pre-procedural troponin elevation. Patients with prior revascularization, heart failure, or who presented with cardiogenic shock, STEMI, or unstable angina were excluded. After propensity matching, outcomes were compared between groups. The primary outcome was major adverse cardiovascular events (MACE: mortality, myocardial infarction, and revascularization) within one year: 3,924 patients with nonobstructive CAD and a troponin obtained prior to angiography were identified (n=1,986 with elevated troponin) and restricted to 1,904 patients after propensity-matching. There was a significantly higher risk of MACE among troponin-positive patients compared with those with a negative troponin (HR 2.37; 95% CI, 1.67 to 3.34). Statin (HR 0.32; 95% CI, 0.22 to 0.49) and ACE inhibitor (HR 0.49; 95% CI, 0.32 to 0.75) therapy after angiography was associated with decreased MACE, while P2Y12 inhibitor, calcium-channel and beta-blocker therapy were not associated with outcomes. In conclusion, Veterans with MINOCA are at increased risk for MACE compared with those with nonobstructive CAD and negative troponin at the time of angiography. Specific medications were associated with a reduction in MACE, suggesting an opportunity to explore novel approaches for secondary prevention in this population. **(Am J Cardiol 2021;146:1−7)**

Nonobstructive coronary artery disease is identified in 5% to 15% of patients presenting with myocardial infarction and is associated with mortality rates up to 5% at one year [1−5]. Proposed causes of myocardial infarction with nonobstructive coronary artery disease (MINOCA) are diverse and include both epicardial and microvascular etiologies [5-9]. Prior studies suggest that traditional cardiovascular risk factors are less prevalent in patients with MINOCA as compared with those with MI due to obstructive coronary artery disease (MI-CAD) [5,7,10,11]. Expert recommendations advocate cause-targeted therapies for patients with a known etiology of MINOCA, but otherwise endorse traditional secondary prevention medications used for MI-CAD.[4,12]

Some analyses have suggested that these medications may not offer benefit for patients with MINOCA, calling into question the routine use of such therapies in this population[8,13−15]. Given the paucity of data for treatment or secondary prevention of MINOCA, we sought to further investigate the relationship between MINOCA and clinical outcomes and the influence of secondary prevention measures. We leveraged data from the Veterans Affairs Healthcare System to describe and compare the characteristics and outcomes of patients with MINOCA as compared with patients with nonobstructive CAD without MI and evaluate the efficacy of cardiovascular medical therapy on outcomes in these populations.

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See page 6 for disclosure information.

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Methods

The Veterans Affairs (VA) Clinical Assessment, Reporting and Tracking (CART) program is a national quality and safety oversight authority for invasive cardiac procedures within the VA Health Care System. As described previously, this mandatory program captures standardized patient and procedural data elements for invasive cardiac procedures. The data elements are derived from previously established data definitions from the National Cardiovascular Data Registry (NCDR), and the dataset is independently assessed for accuracy and validity on a routine basis [16,17]. This study identified all patients over the age of 18 who underwent coronary angiography between October 1, 2008, and September 30, 2017, who had a serum troponin evaluated within the 72 hours prior to angiography and who were found to have non-obstructive CAD. Non-obstructive CAD was defined as stenoses <70% in major epicardial vessels or <50% in the left main coronary artery. In patients who underwent multiple coronary angiograms, the first angiogram was considered the index procedure and was included in the analysis; subsequent angiograms were excluded. Of these patients, those with cardiogenic shock, STEMI, unstable angina, prior PCI, prior CABG, left ventricular fraction (LVEF) <40%, congenital heart disease, or recent cardiac surgery were excluded. Patients who underwent PCI on the same day as the index angiogram, suffered an in-lab death, or who underwent coronary angiography as an outpatient were also excluded. Serum troponin elevation (troponin-positive) was defined as a value > 99th percentile of the reference range in accordance with local testing protocols and assays. Levels below this value were within normal range (troponin-negative). For propensity score matching, missing values were imputed using the median. This study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent.

Patient characteristics, laboratory studies, medications, procedural details, and complications were obtained from CART and the linked VA electronic health record. Angiographic severity of coronary stenoses was determined by the performing angiographer and recorded as previously described [17]. Mortality was ascertained from the VA Information Resource Center Vital Status File, which includes vital data from the Beneficiary Identification Record Locator Subsystem Death File, VA Medicare Vital Status File, and the Social Security Administration Death Master File. One year of follow-up data for the primary composite outcome was available for all subjects in the cohort.

The cohort was divided into 2 groups who underwent coronary angiography: those with an elevated serum troponin value (positive) prior to the procedure and those without troponin elevation (negative). Propensity score matching was used to address differences between these groups. Variables used for matching included demographic information: age, race, ethnicity, gender, height, weight, BMI; co-morbidities: history of MI, congestive heart failure, or cardiogenic shock, valvular heart disease, atrial fibrillation, prior CVA, diabetes, chronic kidney disease, dialysis, renal transplant, peripheral arterial disease, hypertension, hyperlipidemia, family history of CAD, long term obstructive pulmonary disease, sleep apnea, deep vein thrombosis, alcohol use, tobacco use, substance abuse, depression, anxiety, PTSD, other psychiatric history; previous procedures: prior coronary angiography, prior valve intervention, prior cardiac transplant; laboratory studies: LDL, HDL, creatinine, GFR; physical exam findings: heart murmur, extra heart sounds, rales; and mortality prediction scores: Framingham 10 year risk score, NCDR CathPCI risk score [18,19]. Using these variables for adjustment, a multivariable logistic regression was created to identify the propensity of a patient having a positive troponin. The results of this model were used for matching by a greedy 8-to-1 digit matching algorithm[20]. One-to-one matching was performed using propensity scores to account for the observable differences in baseline characteristics between positive and negative troponin groups. Covariate balance of the matched cohort was assessed using standardized mean differences.

Cox proportional hazard models were used to assess the relationship between positive vs. negative troponin levels and major adverse cardiovascular events (MACE; all-cause mortality, myocardial infarction, and revascularization) in the matched cohort. Similar methods were used to assess the influence of beta blockers, statins, ACE inhibitors, calcium channel blockers and P2Y12 inhibitors prescribed within 90 days of the index procedure. Cumulative outcomes were estimated by the Kaplan-Meier method for the positive and negative troponin groups. Finally, to assess for the potential influence of early revascularization on outcomes, a sensitivity analysis was conducted in which patients who underwent PCI within 30 days of the index angiogram were excluded. A new propensity matched cohort was generated from this population, using similar methods and Cox proportional hazards again used to assess outcomes across groups. One year of follow-up data for the primary composite outcome was available for all subjects in the cohort. Data preparation and Cox regression models were generated using SAS software, version 9.4 (SAS Institute, Cary, North Carolina). Descriptive and graphical analysis was performed with R version 3.5.3. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 3,924 patients were included in the analysis (**Figure 1**). There were 1,986 patients in the study population with a positive troponin and 1,201 patients with a negative troponin in the 72 hours preceding angiography. Baseline demographics and clinical co-morbidities are listed in **Table 1**. Angiographic lesion severity was similar between groups (**Supplemental Table 1**). Patients with negative troponin assays prior to angiography were younger, less likely to be of white race, and had lower body mass indices than their troponin-positive counterparts. A greater proportion of patients in the troponin-positive group had congestive heart failure, prior myocardial infarction, chronic kidney disease, dialysis-dependence, cerebrovascular disease, peripheral arterial disease, or atrial fibrillation. Troponin-positive patients had higher rates of beta blocker, ACE inhibitor, P2Y12 inhibitor, and anticoagulant use at baseline compared with troponin-negative patients. Statin use was similar in each group. The median NCDR CathPCI

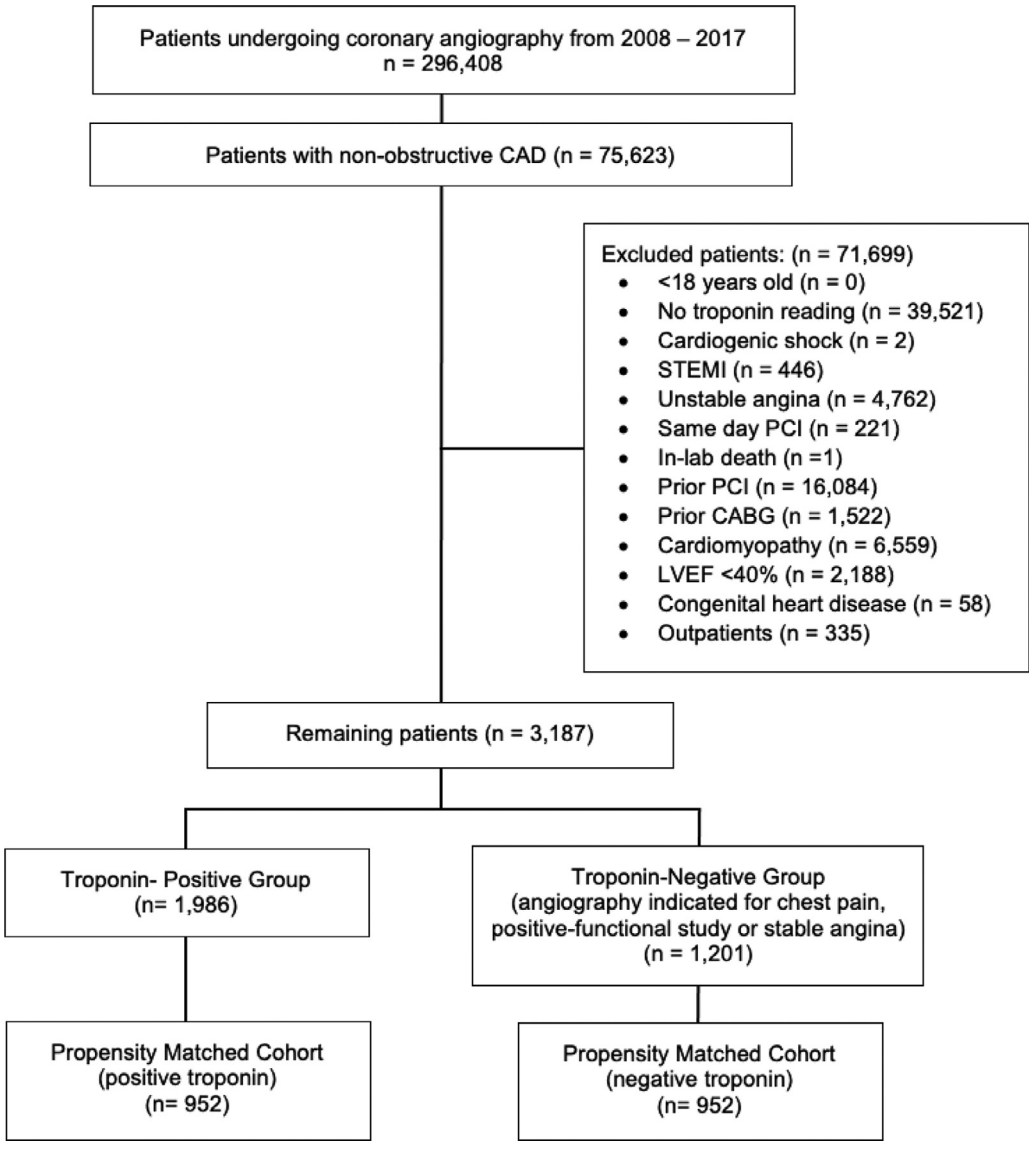

Figure 1. PRISMA diagram of eligible patient population and exclusion criteria.
Abbreviations: CABG, coronary artery bypass graft; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

risk score was 16 (interquartile range [IQR] 10 to 23) and the Framingham 10-year mortality risk was 13% (IQR 8 to 20; **Table 1**).

The primary composite outcome occurred in 351 patients (9%) with 231 deaths, 19 myocardial infarctions, and 101 readmissions for revascularization during 1 year of follow-up. There were no deaths during angiography and no significant differences in procedural complications between subgroups.

Factors associated with the presence of a positive serum troponin prior to angiography included prior myocardial infarction, presence of rales on physical exam, and being of non-Hispanic ethnicity (**Supplemental Table 2**). Characteristics associated with negative troponin values prior to angiography were a history of peripheral arterial disease, a history of hyperlipidemia, and a history of prior cardiac catheterization. After matching, 1,283 patients were excluded from the analysis (40%), resulting in a total of 952 matched pairs of troponin-positive and troponin-negative patients. Standardized mean differences demonstrated satisfactory matching between groups (**Supplemental Table 3**). Among matched troponin-positive patients there were 105 MACE events, comprised of 58 deaths, 9 MIs, and 38 hospitalizations for revascularization. Among matched troponin-negative patients, there were 46 MACE events, comprised of 30 deaths, 1 MI, and 15 hospitalizations for revascularization (**Supplemental Table 4; Figure 2**, log-rank p <0.001). The hazard of MACE was significantly elevated for patients with a positive troponin (HR 2.37; 95% CI, 1.67-3.34).

Within 90 days of the index angiogram, patients most commonly received statins (57%), beta blockers (45%), and ACE inhibitors (35%), with less than one quarter receiving calcium channel blockers (22%) or P2Y12 inhibitors (12%;

Table 1
Baseline patient demographics and characteristics

Variable	Overall(N=3187)	Troponin+(N=1986)	Troponin-(N=1,201)	p-value
Age (years)	64 (59-70)	64 (59-71)	62 (56-67)	<0.001
Male gender	3011 (94%)	1877 (95%)	1134 (95%)	0.98
Body Mass Index (kg/m^2)	29.4 (25.6-33.8)	28.8 (24.9-33.3)	30.2 (26.2-34.4)	<0.001
Race				
White	2244 (70%)	1352 (68%)	892 (74%)	
Black	759 (24%)	24 (26%)	235 (20%)	
Other/unknown	184 (6%)	110 (6%)	74 (6%)	
Hispanic ethnicity	153 (5%)	109 (5%)	44 (4%)	
Prior myocardial infarction	382 (12%)	328 (17%)	54 (4%)	<0.001
Congestive heart failure	708 (22%)	575 (29%)	133 (11%)	<0.001
Left ventricular EF (%)	60 (55-65)	60 (55-65)	59 (62-65)	0.001
History of cardiogenic shock	11 (0%)	11 (1%)	0 (0%)	0.02
Valvular heart disease	352 (11%)	279 (14%)	73 (6%)	0.03
Atrial fibrillation	506 (16%)	387 (19%)	119 (10%)	<0.001
Cerebrovascular accident	429 (13%)	325 (16%)	104 (9%)	<0.001
CKD (GFR<60 ml/min)	605 (19%)	467 (24%)	138 (11%)	<0.001
Dialysis-dependence	82 (3%)	77 (4%)	5 (0%)	<0.001
Diabetes	1205 (38%)	756 (38%)	428 (36%)	0.73
Peripheral arterial disease	414 (13%)	290 (15%)	124 (10%)	0.001
Hypertension	2719 (85%)	1707 (86%)	1012 (84%)	0.21
Hyperlipidemia	2505 (79%)	1505 (76%)	1000 (83%)	<0.001
Family history of CAD	441 (14%)	235 (12%)	206 (17%)	<0.001
COPD	784 (25%)	530 (27%)	254 (21%)	0.001
Sleep apnea	732 (23%)	452 (23%)	280 (23%)	0.75
Deep vein thrombosis	138 (4%)	106 (5%)	32 (3%)	<0.001
Alcohol use	474 (15%)	313 (16%)	161 (13%)	0.08
Tobacco use	1944 (61%)	1249 (63%)	695 (58%)	0.01
Substance use	309 (10%)	216 (11%)	93 (8%)	0.01
Depression	1102 (35%)	674 (34%)	428 (36%)	0.35
Anxiety	419 (13%)	240 (12%)	179 (15%)	0.03
PTSD	614 (19%)	351 (18%)	263 (22%)	0.004
Prior coronary angiography	551 (17%)	326 (16%)	225 (19%)	0.10
Prior valvular surgery/intervention	47 (1%)	37 (2%)	10 (1%)	0.03
Precordial murmur	280 (9%)	225 (11%)	55 (5%)	<0.001
Extra heart sound	71 (2%)	56 (3%)	15 (1%)	0.01
Rales	117 (4%)	106 (5%)	11 (1%)	<0.001
Troponin (ng/mL)				
Troponin I	0.18 (0.04-1.46)	0.78 (0.19-3.12)	0.021 (0.013-0.04)	<0.001
Troponin T	0.03 (0.01-0.22)	0.22 (0.11-0.48)	0.01 (0.01-0.03)	<0.001
BNP (pg/mL)	115 (35-459)	209 (63-653)	41 (18-104)	<0.001
NT-pro BNP (pg/mL)	375 (84-2450)	1170 (207-3930)	64 (31-191)	<0.001
Creatinine (mg/dL)	1.0 (0.85-1.2)	1.0 (0.86-1.3)	1.0 (0.84-1.2)	<0.001
GFR (mL/min)	80 (64-93)	79 (60-93)	80 (69-93)	<0.001
LDL (mg/dL)	95 (74-119)	95 (73-119)	97 (76-121)	0.03
HDL (mg/dL)	41 (34-49)	41 (34-50)	40 (34-48)	0.01
NCDR CathPCI risk score	16 (10-23)	18 (12-26)	14 (8-18)	<0.001
Framingham risk score	13 (8-20)	13 (10-20)	13 (8-20)	<0.001
Beta blocker	840 (26%)	478 (24%)	362 (30%)	<0.001
ACE inhibitor	819 (26%)	517 (26%)	302 (25%)	0.61
Calcium channel blocker	562 (18%)	367 (18%)	195 (16%)	0.12
Statin	1180 (37%)	660 (33%)	520 (43%)	<0.001
P2Y12 inhibitor	110 (3%)	96 (5%)	14 (1%)	<0.001
Anticoagulant	172 (5%)	131 (7%)	41 (3%)	<0.001

Abbreviations: ACE = angiotensin-converting-enzyme; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; BNP = brain natriuretic peptide; EF = ejection fraction; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTSD = post-traumatic stress disorder. Numbers are presented as N (%) or median (IQR).

Supplemental Table 5). Rates of medication use were similar between troponin-positive and troponin-negative patients, with the exception of P2Y12 inhibitors (20% vs. 3%, p<0.001). The risk of MACE was significantly lower among patients treated with a statin and patients treated with an ACE inhibitor, while use of calcium channel blockers, beta blockers, and P2Y12 inhibitors were not associated with MACE (**Table 2**).

A sensitivity analysis cohort excluded 24 patients who underwent PCI within 30 days of index angiography and

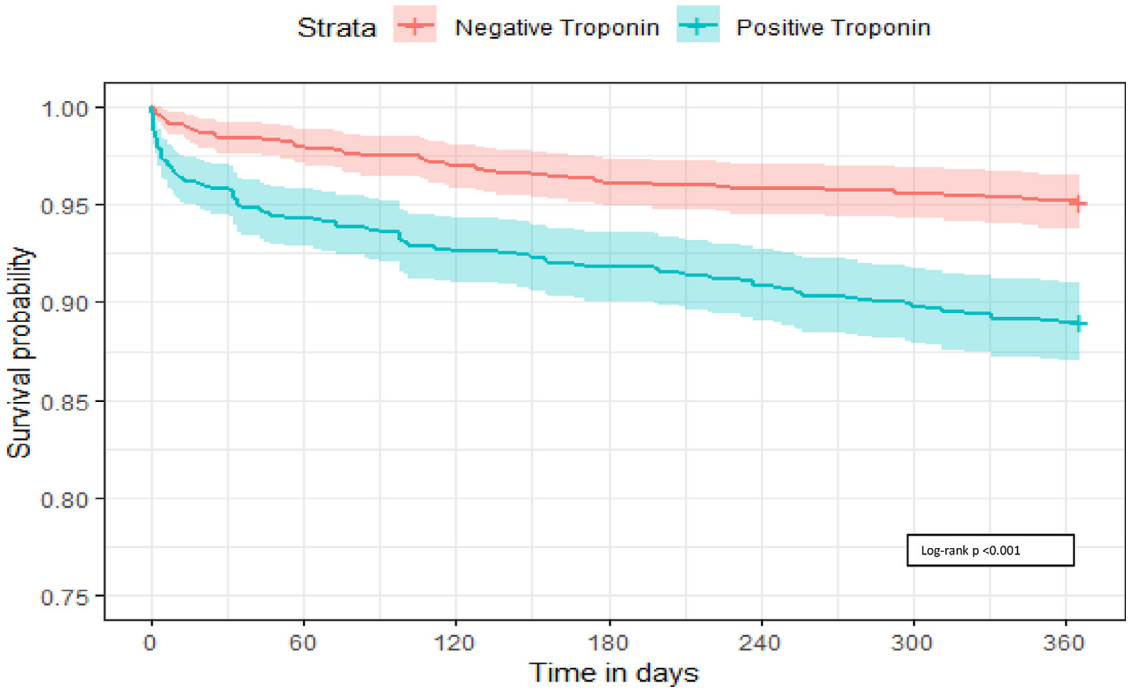

Figure 2. Kaplan-Meier analysis of major adverse cardiac events in the matched cohort.

underwent repeat propensity analysis, resulting in 940 matched pairs of troponin-positive and troponin negative patients (**Supplemental Table 6**). Within this subgroup, the hazard ratio of MACE for the troponin-positive subgroup was 1.81 (95% CI, 1.25 to 2.62) (**Supplemental Figure 1**).

Discussion

The present study compared the characteristics and one-year outcomes of patients with MINOCA to those with non-obstructive CAD without MI in a national, integrated healthcare system. In a propensity-matched analysis we found that positive troponin within the 72 hours preceding angiography was associated with a greater than two-fold increase in the hazard of death, MI, or revascularization. Post-angiography treatment with statins and ACE inhibitors was associated with a decreased risk of MACE during follow-up, while use of calcium channel blockers, beta blockers and P2Y12 inhibitors had no significant association with outcomes. These results suggest that while MINOCA is associated with poor outcomes, treatment with statins and ACE inhibitors may mitigate risk in these patients.

Table 2
Association of medication prescription with major adverse cardiovascular events

	HR	95% CI
Statin	0.34	0.23-0.51
ACE inhibitor	0.51	0.33-0.79
Calcium channel blocker	0.63	0.38-1.04
Beta blocker	1.09	0.73-1.62
P2Y12 inhibitor	1.02	0.58-1.80

Abbreviations: CI = confidence interval; HR = hazard ratio.

Our finding that MINOCA confers a significant risk of mortality and morbidity consistent with prior analyses. The observed 12-month mortality rate of 6% is consistent with other published reports, despite a higher prevalence of co-morbid conditions in our study population[5,8,13]. Although prior analyses have demonstrated that patients with MINOCA have a decreased risk of death or cardiovascular events compared with those with MI-CAD, less is understood regarding the prognosis of MINOCA patients as compared with patients with nonobstructive CAD without MI[5,11,21]. Our analysis demonstrates that MINOCA patients are at higher risk of long-term adverse events than patients with nonobstructive CAD without MI, even with a high burden of co-morbid conditions. Consistent with prior findings, these data suggest that troponin elevation represents a level of medical acuity that is not captured by coronary anatomy or co-morbidities alone [22,23]. These findings together underscore the importance of moving away from the traditional dichotomous approach to coronary artery disease, characterized by obstructive or nonobstructive disease states. Prior work has suggested that stable CAD provides a continuum of risk and MINOCA likely represents yet another facet of an increasingly complex understanding of myocardial ischemia [24].

Prior studies have suggested that the atherosclerotic burden of disease in MINOCA patients is generally minimal, however the majority of described secondary prevention strategies focus on traditional antithrombotic pathways[4]. Furthermore, multiple analyses have demonstrated conflicting results on the efficacy of secondary prevention medications for prevention of adverse events following MINOCA [8,13–15]. Our finding that statin and ACE inhibitor therapy are associated with a reduction in MACE is consistent with these data, as was a lack of benefit seen with the

use of beta blockers and dual antiplatelet therapy. Both ACE inhibitors and statins have demonstrated anti-inflammatory properties in other disease states, raising the possibility of pleiotropic effects for these agents in MINOCA beyond the known mechanisms for benefit in MI-CAD. Additionally, prior studies have suggested that ACE inhibitors and statins may improve endothelial dysfunction, one of the proposed underlying mechanisms for MINOCA[25,26]. In evaluation of other potential targeted therapies etiologies for MINOCA like coronary vasospasm, we also assessed the impact of calcium channel blocker use. In a cohort of 396 patients with MINOCA, Choo et al. found that 95 (24%) demonstrated vasospasm on provocative testing, but neither the presence of vasospasm or treatment with calcium channel blockers was associated with mortality [13]. In our analysis, we found a numerically but not statistically significant reduction in MACE among patients treated with calcium channel blockers. Although our results did not reach significance, the noted trend may result from the higher prevalence of known triggers of vasospasm like cigarette smoking, alcohol, and stimulant use in this cohort[27,28]. In summary, these findings suggest that an etiology-tailored approach to the use of these medications after MINOCA may benefit patients.

This study benefits from its large size and detailed patient data derived from a nationally integrated medical system. However, the results must be interpreted in the context of the study's limitations. First, there is the possibility of residual or unmeasured confounding inherent in the study's observational design. Robust statistical methodology including propensity matching were used to limit these potential influences. Patients presenting with cardiogenic shock, STEMI, or unstable angina were excluded given that increased clinical suspicion for acute coronary syndrome due to plaque rupture may influence angiographic assessments and decisions to revascularize[29–31]. This was done purposefully to create a more homogeneous cohort, but may have limited the observed event rates of the study. Data regarding utilization of aspirin and its effect on outcomes were not available because aspirin is considered an over-the-counter medication in the VA system and its prescription is not consistently tracked. Additionally, the results of vasospasm testing, coronary intravascular imaging, or cardiac magnetic resonance studies were not widely available, limiting our ability to identify the etiology of MINOCA or comment on the strategy of tailoring therapies to suspected or confirmed etiologies. However, the cause of MINOCA is infrequently determined in clinical practice[5]. Moreover, subgroup analyses of our cohort by MINOCA etiology are unlikely to provide robust data, due to further reductions in sample size. Finally, the findings of this study may not be generalizable to broader populations of MINOCA with higher representations of female gender and non-caucasian race[5,8,9,32].

In conclusion, Veterans with MINOCA are at increased risk of death, myocardial infarction, and revascularization as compared with patients with nonobstructive CAD without MI. Although not all secondary prevention measures were independently associated with MACE, these results suggest that there may be a role for statins and ACE inhibitors after MINOCA in improving outcomes for these patients.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.015.

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