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# Nonobstructive Coronary Artery Disease and Risk of Myocardial Infarction

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## Abstract

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**IMPORTANCE—**Little is known about cardiac adverse events among patients with nonobstructive coronary artery disease (CAD).

**OBJECTIVE—**To compare myocardial infarction (MI) and mortality rates between patients with nonobstructive CAD, obstructive CAD, and no apparent CAD in a national cohort.

**DESIGN, SETTING, AND PARTICIPANTS—**Retrospective cohort study of all US veterans undergoing elective coronary angiography for CAD between October 2007 and September 2012 in the Veterans Affairs health care system. Patients with prior CAD events were excluded.

**EXPOSURES—**Angiographic CAD extent, defined by degree (no apparent CAD: no stenosis >20%; nonobstructive CAD: ≥1 stenosis ≥20% but no stenosis ≥70%; obstructive CAD: any stenosis ≥70% or left main [LM] stenosis ≥50%) and distribution (1,2, or 3 vessel).

**MAIN OUTCOMES AND MEASURES—**The primary outcome was 1-year hospitalization for nonfatal MI after the index angiography. Secondary outcomes included 1-year all-cause mortality and combined 1-year MI and mortality.

**RESULTS—**Among37 674 patients, 8384 patients (22.3%) had nonobstructive CAD and 20 899 patients (55.4%) had obstructive CAD. Within 1 year, 845 patients died and 385 were rehospitalized for MI. Among patients with no apparent CAD, the 1-year MI rate was 0.11% (n = 8, 95% CI, 0.10%–0.20%) and increased progressively by 1-vessel nonobstructive CAD, 0.24% (n = 10, 95% CI, 0.10%–0.40%); 2-vessel nonobstructive CAD, 0.56% (n = 13, 95% CI, 0.30%–1.00%); 3-vessel nonobstructive CAD, 0.59% (n = 6, 95% CI, 0.30%–1.30%); 1-vessel obstructive CAD, 1.18% (n = 101, 95% CI, 1.00%–1.40%); 2-vessel obstructive CAD, 2.18% (n = 110, 95% CI, 1.80%–2.60%); and 3-vessel or LM obstructive CAD, 2.47% (n = 137, 95% CI, 2.10%–2.90%). After adjustment, 1-year MI rates increased with increasing CAD extent. Relative to patients with no apparent CAD, patients with 1-vessel nonobstructive CAD had a hazard ratio (HR) for 1-year MI of 2.0 (95% CI, 0.8–5.1); 2-vessel nonobstructive HR, 4.6 (95% CI, 2.0–10.5); 3-vessel nonobstructive HR, 4.5 (95% CI, 1.6–12.5); 1-vessel obstructive HR, 9.0 (95% CI, 4.2–19.0); 2-vessel obstructive HR, 16.5 (95% CI, 8.1–33.7); and 3-vessel or LM obstructive HR, 19.5 (95% CI, 9.9–38.2). One-year mortality rates were associated with increasing CAD extent, ranging from 1.38% among patients without apparent CAD to 4.30% with 3-vessel or LM obstructive CAD. After risk adjustment, there was no significant association between 1- or 2-vessel nonobstructive CAD and mortality, but there were significant associations with mortality for 3-vessel nonobstructive CAD (HR, 1.6; 95% CI, 1.1–2.5), 1-vessel obstructive CAD (HR, 1.9; 95% CI, 1.4–2.6), 2-vessel obstructive CAD (HR, 2.8; 95% CI, 2.1–3.7), and 3-vessel or LM obstructive CAD (HR, 3.4; 95% CI, 2.6–4.4). Similar associations were noted with the combined outcome.

**CONCLUSIONS AND RELEVANCE—**In this cohort of patients undergoing elective coronary angiography, nonobstructive CAD, compared with no apparent CAD, was associated with a significantly greater 1-year risk of MI and all-cause mortality. These findings suggest clinical importance of nonobstructive CAD and warrant further investigation of interventions to improve outcomes among these patients.

Nonobstructive coronary artery disease (CAD) is atherosclerotic plaque that would not be expected to obstruct blood flow or result in anginal symptoms. Although such lesions are relatively common, occurring in 10% to 25% of patients undergoing coronary

angiography,[1,2] their presence has been characterized as “insignificant” or “no significant CAD” in the medical literature.[3–6] However, this perception of nonobstructive CAD may be incorrect, because prior studies have noted that the majority of plaque ruptures and resultant myocardial infarctions (MIs) arise from nonobstructive plaques.[7–13]

Despite the prevalence of nonobstructive CAD identified by coronary angiography, little is known about its risk of adverse outcomes. The few studies that do exist focus primarily on patients with MI[3,4] and thus are less informative about patients with stable nonobstructive CAD. A primary reason behind this lack of knowledge is lack of data. To date, almost all coronary angiography registries include obstructive CAD only.[14] The few registries that do include patients with nonobstructive CAD lack longitudinal outcomes data.[15] More data on nonobstructive CAD patients and their longitudinal outcomes are essential for understanding their risks for adverse cardiac outcomes and potential therapeutic implications.

This study evaluated the hypothesis that increasing CAD extent across the continuum of nonobstructive and obstructive CAD is associated with increasing rates of MI and all-cause mortality. To test this hypothesis, we used data from the national Veterans Affairs (VA) Clinical Assessment, Reporting, and Tracking (CART) program, which records anatomic data from all coronary angiograms performed in the VA health care system and tracks patients’ longitudinal outcomes. We assessed the prevalence of nonobstructive and obstructive CAD extent and assessed its association with 1-year hospitalization for nonfatal MI and all-cause mortality rates.

## Methods

Data for this analysis were from the VA CART program, which is a national clinical quality program for all VA cardiac catheterization laboratories.[16] This program uses a clinical software application, embedded in the VA electronic health record (EHR), to capture standardized patient and procedural data for all coronary procedures performed in VA catheterization laboratories nationwide. Data elements in the application are derived from the American College of Cardiology’s National Cardiovascular Data Registry (NCDR) data definitions.[15] Quality checks of the CART data are periodically conducted for completeness and accuracy, and its data validity, completeness, and timeliness have been previously demonstrated.[17]

To capture longitudinal patient data, CART data are combined with other data from the VA patient EHR. These data include vital status, inpatient hospitalizations, outpatient clinic visits, pharmacy prescriptions and refills, and laboratory testing. In addition, the data set is merged with VA claims data from those hospitalizations at non-VA facilities where the VA pays for the veterans’ care. Institutional review board and VA research and development approvals were obtained for the creation of the data set and for this particular study. The Colorado multiple institutional review board provided a waiver of consent and approval for this study.

### Study Cohort

The analysis included all VA patients undergoing elective coronary angiography for CAD indications (chest pain, stable angina, ischemic heart disease, or positive functional study) between October 2007 and September 2012 in any of the 79 VA cardiac catheterization laboratories. Positive functional study was defined as any cardiac stress test indicative of ischemia. Patients with known prior CAD events–defined as prior MI, acute coronary syndrome (ACS), or coronary revascularization–were excluded. For patients receiving multiple coronary angiograms during our study time period, the first angiogram was used to characterize CAD extent.

### Independent Variables

Consistent with standard definitions of flow-limiting stenoses,[18–20] nonobstructive CAD was defined as a coronary artery stenosis 20% or greater but less than 50% in the left main coronary artery or a stenosis 20% or greater but less than 70% in any other epicardial coronary artery, as recorded by the clinician in the catheterization report. Obstructive CAD was defined as any stenosis 50% or greater in the left main coronary artery, 70% or greater in any other coronary artery, or both. No apparent CAD was defined as all coronary stenoses less than 20% or luminal irregularities.

We then categorized each patient by his or her CAD extent. To accomplish this, we categorized each patient by CAD severity in a single, double, or triple-vessel distribution. We defined vessel distribution by the left anterior descending artery and its tributaries, the left circumflex artery and its tributaries, and the right coronary artery and its tributaries. Patients with isolated 20% to 49% left main stenosis were included with the 1-vessel nonobstructive CAD patients. Patients with 50% or greater left main coronary artery stenosis were included with the 3-vessel obstructive CAD patients. For each vascular distribution, we determined the maximal stenosis present and classified that distribution as no apparent CAD, nonobstructive CAD, or obstructive CAD, as defined in the preceding paragraph. In total, we created 7 categories of CAD extent: no apparent CAD; 1-, 2-, and 3-vessel nonobstructive CAD; and 1-, 2-, and 3-vessel obstructive CAD.

### Outcomes

The primary outcome was 1-year hospitalization for nonfatal MI after the index angiography. Myocardial infarction was defined by a primary diagnosis *International Classification of Diseases, Ninth Revision (ICD-9)* code of 410.xx in VA inpatient and VA fee-based data files. To account for those veterans who are “dual covered” with Medicare and VA benefits and may have been hospitalized in a non-VA hospital using their Medicare benefits, we also included all Medicare hospitalizations for MI through calendar year 2011 in our cohort, using the most recent Centers for Medicare & Medicaid Services (CMS) data files. Data files from the VA and CMS were linked using scrambled Social Security numbers for individual patients. Secondary outcomes included 1-year all-cause mortality and combined 1-year MI and mortality. Mortality was measured using VA vital status data.

## Statistical Analyses

Characteristics of patients (demographics, comorbidities), procedural data (eg, indications for angiography), postangiography cardiac medications, and postangiography revascularization treatments were collected and compared by CAD extent. Categorical data were compared using $\chi^2$ tests and continuous data using Mann-Whitney Wilcoxon non-parametric tests.

Rates of MI, all-cause mortality, and the combined outcome during the full study period were calculated and compared by CAD extent using log-rank tests and Kaplan-Meier curves. Unadjusted outcome rates were calculated using Kaplan-Meier estimates to include the full study cohort with its differential censoring. Cox regression modeling was used to adjust for covariates selected from prior studies and a priori clinical reasoning.[15,17] All outcomes were censored at 1 year. Patients with no apparent CAD were used as the reference group.

A robust estimator of the covariance matrix was used to account for clustering by site.[21] Model covariates included demographics (age, sex, race), CAD risk factors (hypertension, hyperlipidemia, diabetes, tobacco use, obesity), Framingham 10-year cardiovascular disease risk, other comorbidities (congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral arterial disease, post-traumatic stress disorder, depression, sleep apnea, chronic kidney disease, dialysis), angiography indication (chest pain, positive functional study, ischemic heart disease, stable angina), postangiography cardiac medications (statins, β-blockers, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers), and postangiography revascularization (none, coronary artery bypass graft surgery, percutaneous coronary intervention).

Race was defined as white or nonwhite. Nonwhite race included American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian, or Other Pacific Islander. Racial and ethnicity classifications were based on patient self-report, where possible, and performed in accord with VA best practices for data classification.[22] Obesity was defined as a body mass index of 30 or greater (calculated as weight in kilograms divided by height in meters squared). Framingham risk was calculated using methods previously described[20] and defined as low (<10% 10-year predicted risk of cardiac adverse events), intermediate (10%–20% 10-year predicted risk of cardiac adverse events), and high (>20% 10-year predicted risk of cardiac adverse events). Aspirin use could not be reliably calculated, as most veterans obtain those medications from outside, over-the-counter pharmacies rather than from a VA pharmacy.

We conducted several sensitivity analyses to test the robustness of our findings. First, to incorporate all available coronary anatomic data from CART in our classification of CAD extent, we categorized CAD by classifying each major coronary territory as no apparent CAD, nonobstructive, or obstructive using the definitions listed earlier in this section, thus creating 10 CAD categories. We then compared increasing CAD extent, as defined by these 10 categories, to our outcomes using a linear regression model that adjusted for the same covariates used in our primary analysis. Second, our initial analyses noted that a small number of patients with no apparent CAD and nonobstructive CAD (n = 110, 0.3%) underwent subsequent revascularization, indicating that they had at least 1 stenosis that the

treating clinician determined appropriate for re-vascularization. To determine if these patients–who could not be definitively classified into no apparent, nonobstructive, or obstructive CAD categories based on the data–affected the overall results, we excluded them and reran our primary analyses. Third, we had CMS data only through the end of calendar year 2011, because of the latency with which CMS makes their data available publicly. To determine whether inclusion of these data altered our primary findings, we reran our primary analyses excluding CMS data.

In addition to our primary and sensitivity analyses, 3 secondary analyses were also conducted. First, to determine if increasing degrees of nonobstructive CAD severity were associated with outcomes in a progressive manner, nonobstructive CAD was subdivided into mild (maximal coronary stenosis of 20%–49%) and moderate nonobstructive CAD (maximal coronary stenosis of 50%–69%), in line with standard definitions regarding CAD severity.[23] The analysis was restricted to those patients who had sufficient coronary anatomic information to determine mild and moderate nonobstructive CAD. We then conducted unadjusted and adjusted time-to-event analyses, using no apparent CAD as the referent group.

Second, we conducted prespecified subgroup analyses among patients with diabetes in our cohort, because prior cardiac computed tomography (CT) investigations among patients with nonobstructive CAD found that diabetes significantly modified outcomes.[24] Diabetes was determined from VA data files. Stratified analyses and interaction testing were performed. To assess for interaction between diabetes and CAD extent,andbetween symptoms and CAD extent, separate Cox models were fitted with the interaction term and main effect, adjusting for covariates. Wald tests with 6 *df* were used to test the interaction term.

Third, we conducted a similar analysis among symptomatic patients in our cohort, again because prior CT literature demonstrated effect modification by symptoms among patients with nonobstructive CAD.[25,26] Cardiac symptoms were determined by the presence of either stable angina or chest pain as the primary angiography indication. Stratified analyses and interaction testing were performed.

Because we cross-referenced CART data with VA patient data files, most variables were missing in less than 5% of cases. One exception was data on race, which we imputed using the SAS procedure PROC MI. All analyses were done in SAS version 9.3 (SAS Institute). Significance testing was 2-sided, and all *P* values <.05 were considered statistically significant.

## Results

During the study period, 37 674 patients underwent elective coronary angiography for indications related to CAD as characterized by the treating clinician (Table 1 and Table 2). Of those, 8391 (22.3%) patients had no apparent CAD; 8384 (22.3%) patients had nonobstructive CAD (1-vessel: 4646 [12.3% of total patients], 2-vessel: 2605 [6.9%], 3-vessel: 1133 [3.0%]); and 20 899 (55.4%) patients had obstructive CAD (1-vessel: 9411 [25.0% of total patients], 2-vessel: 5452 [14.5%], 3-vessel or left main [LM]: 6036

[16.0%]). The majority of patients underwent angiography for chest pain. Age, cardiovascular risk factors (eg, hypertension, hyperlipidemia, and diabetes), and Framingham risk scores all increased with increasing CAD extent. In addition, the frequency of prescriptions for postangiography cardiovascular medications and rates of coronary revascularization also increased with CAD extent.

## Outcomes

In unadjusted analyses, 1-year MI rates progressively increased with increasing CAD extent, ranging from 0.11% among patients with no apparent CAD to 2.47% among patients with 3-vessel or LM obstructive CAD (Table 3 and Figure 1). After risk adjustment using the covariates described in the “Methods” section, there was no association between 1-vessel nonobstructive CAD and MI, but there were significant associations with MI for 2-vessel nonobstructive; 3-vessel nonobstructive; and 1-, 2-, and 3-vessel or LM obstructive CAD (Figure 2).

Similar relationships were noted when both 1-year all-cause mortality and combined MI and mortality outcomes were examined. One-year mortality rates demonstrated a largely progressive relationship with increasing CAD extent, ranging from 1.38% among patients without apparent CAD to 4.30% among patients with 3-vessel or LM obstructive CAD (Table 3 and Figure 1). After risk adjustment, there was no association between 1-vessel or 2-vessel nonobstructive CAD and mortality, but there were significant associations with mortality for 3-vessel nonobstructive and 1-, 2-, and 3-vessel or LM obstructive CAD (Figure 2).

Similarly, combined MI and mortality outcomes also demonstrated a largely progressive relationship with increasing CAD extent, ranging from 1.48% for patients with no apparent CAD to 6.19% for patients with 3-vessel or LM obstructive CAD (Table 3 and Figure 1). After risk adjustment, there was no association between 1-vessel or 2-vessel nonobstructive CAD and mortality, but there were significant associations with combined outcomes for 3-vessel non-obstructive and 1-, 2-, and 3-vessel or LM obstructive CAD (Figure 2). Sensitivity analyses exploring additional categorization of CAD extent, exclusion of nonobstructive CAD patients undergoing coronary revascularization, and exclusion of Medicare outcomes were conducted as described in the “Methods” section. None of the analyses materially affected our findings for any of the outcomes.

## Secondary Analyses

Three subgroup analyses were conducted: outcomes among patients with mild/moderate nonobstructive CAD, patients with diabetes, and symptomatic patients. Among 8740 patients with nonobstructive CAD, 4913 (56.2%) had mild nonobstructive CAD, and 3827 (43.8%) had moderate non-obstructive CAD. All unadjusted outcomes increased in progressive fashion in association with mild to moderate non-obstructive CAD (eTable in the Supplement). After risk adjustment, all outcomes, with the exception of mild non-obstructive CAD and 1-year mortality, significantly increased with increasing nonobstructive CAD extent (eFigure 1 in the Supplement). Among 37 674 patients in the study cohort, 15 699 (41.7%) had diabetes. Adjusted outcome rates increased with increasing CAD extent but

did not significantly differ by diabetes status in interaction testing (eFigure 2 in the Supplement). Among 37 674 patients in the study cohort, 25 856 (68.6%) were symptomatic. Adjusted outcome rates increased with increasing CAD extent but did not significantly differ by symptomatic status in interaction testing (eFigure 3 in the Supplement).

## Discussion

This study assessed the risk of patients with nonobstructive CAD for 1-year MI and all-cause mortality rates, compared with those with no apparent CAD and obstructive CAD. The 1-year MI risk progressively increased by CAD extent, rather than abruptly increasing between nonobstructive and obstructive CAD. Moreover, patients with nonobstructive CAD had an associated risk of MI that was 2- to 4.5-fold greater than among those with no apparent CAD. Similar observations were noted with 1-year mortality and combined outcomes. These findings highlight a need to recognize that nonobstructive CAD is associated with significantly increased risk for MI, consistent with prior biologic studies indicating that a majority of MIs are related to nonobstructive stenoses.[7–13] Correspondingly, these results reveal the limitations of a dichotomous characterization of angiographic CAD into “obstructive” and “nonobstructive” to predict MI and highlight the importance of preventive strategies such as pharmacotherapy treatments and lifestyle modifications to mitigate these risks.

Historically, obstructive CAD has been the primary focus in CAD management because of its role in causing cardiac ischemia and accompanying anginal symptoms.[27,28] In addition, obstructive CAD usually corresponds to extensive CAD, which is associated with higher MI rates. However, the recognition that ruptured plaque, rather than occlusive plaque, is the genesis for most MIs,[7,9,12,13,29] along with the recognition that the majority of ruptured plaques arise from nonobstructive CAD,[8,10,11,30] suggests that nonobstructive CAD is associated with significant risk for MI and all-cause mortality and provided the rationale for this investigation.[2,31]

The ability to explore cardiac outcomes among patients with nonobstructive CAD has been limited by insufficient data about both the disease and its outcomes. Most trials and registries in CAD have been limited to patients with obstructive CAD.[14,32] Furthermore, those registries that do collect data about patients with nonobstructive disease, such as the American College of Cardiology’s NCDR CathPCI clinical registry, are limited to in-hospital outcomes and cannot assess long-term adverse clinical events.[15] The VA CART database overcomes these limitations by collecting patient and procedural information about all coronary angiograms conducted in the national VA health care system and links that information to long-term outcomes. Accordingly, this database provides a unique opportunity to study the association between nonobstructive CAD and longer-term adverse events.

To our knowledge, this study provides the most comprehensive assessment of the risks associated with non-obstructive CAD demonstrated during elective coronary angiography. Prior studies have assessed outcomes among MI patients with nonobstructive CAD noted

during diagnostic angiography, but this patient population is small (approximately 5%–10% of all MI patients) and clinically very different from stable patients undergoing elective angiography.[3,4] Studies of nonobstructive CAD have also been conducted among patients undergoing cardiac CT imaging. Although some studies are conflicting, the majority of cardiac CT studies suggest a significant, progressive increase in the risk of major adverse cardiac events with increasing extent of CAD.[33–36] Our study complements these findings by demonstrating the association between nonobstructive CAD and adverse cardiac outcomes using the predominant method of CAD diagnosis in current clinical practice—coronary angiography.

The results of this study support the concept that nonobstructive CAD is not "insignificant"[37] but rather is associated with a significant and quantifiable risk for cardiovascular morbidity and mortality. This suggests that the traditional dichotomous framework for CAD–useful for characterizing and managing ischemia and cardiac symptoms–should not be applied to MI and mortality risks inherent in CAD. Rather, overall CAD extent should be considered a better proxy for both prognosis and management decisions. Some investigators have previously proposed angiographic burden scores and correlated increasing scores with increasing CAD risk.[38,39] Further investigations should focus on the best methods of quantifying CAD extent and correlating it with subsequent MI and mortality rates.

In addition to risk characterization, efforts are needed to understand the best methods for risk mitigation. To date, the major cardiac prevention studies have required either obstructive CAD or a cardiac clinical event for inclusion. The stable nonobstructive CAD patient population was systematically excluded from these studies. Thus, empirical evidence is lacking as to whether these patients benefit from the prevention therapies recommended for their obstructive CAD counterparts. Prior observational studies have found that CAD secondary prevention therapies are prescribed for patients with nonobstructive CAD, although less frequently than for patients with obstructive CAD.[37,40] However, randomized clinical studies of therapies such as antiplatelet agents and statins in patients with clearly defined nonobstructive CAD are needed.

Several potential limitations of this study deserve consideration. First, CART data are recorded directly by the clinician performing the angiogram. As such, misclassification of the degree of CAD severity and its distribution is possible. However, this individual characterization of CAD extent, with its inherent inaccuracies, is standard clinical care, accurately reflects real-world CAD categorization, and thus informs contemporary clinical practice. Second, criteria by which patients are selected to undergo coronary angiograms are variable and likely do not reflect the prevalence of nonobstructive CAD among patients not undergoing angiography. However, the intent of our study was to provide information about the association of adverse outcomes among nonobstructive CAD patients identified at angiography, rather than this broader population.

Third, our association between CAD extent and MI and mortality rates could be confounded by other factors than CAD burden. We used regression modeling that incorporated major demographic, clinical, and treatment variables known to correspond to both CAD and

adverse events. Nonetheless,several variables, such as aspirin use, were not available. As with all observational studies, there is a possibility of unmeasured confounding. Fourth, because cause of death is not available in VA data sets, all-cause mortality was assessed, but cardiac-specific mortality could not be separately evaluated as an additional outcome. Fifth, classification of patients as symptomatic or asymptomatic in secondary analysis relied on the angiographic indication recorded in CART, rather than a direct assessment of symptoms.

Sixth, given the latency with which CMS hospitalization data are reported, we were unable to measure CMS MI rates after December 2011 in our cohort. As a result, we likely under-reported MI rates. However, sensitivity analyses excluding all CMS data from our cohort did not materially change our primary findings, supporting that the CMS MI rates were not differential by CAD extent. Seventh, our findings among VA patients undergoing angiography may not generalize to other populations. As such, our analyses should be replicated in other populations.

## Conclusions

In this cohort of patients undergoing elective coronary angiography, nonobstructive CAD, compared with no apparent CAD, was associated with a significantly greater 1-year risk of MI and all-cause mortality. These findings suggest clinical importance of nonobstructive CAD and warrant further investigation of interventions to improve outcomes among these patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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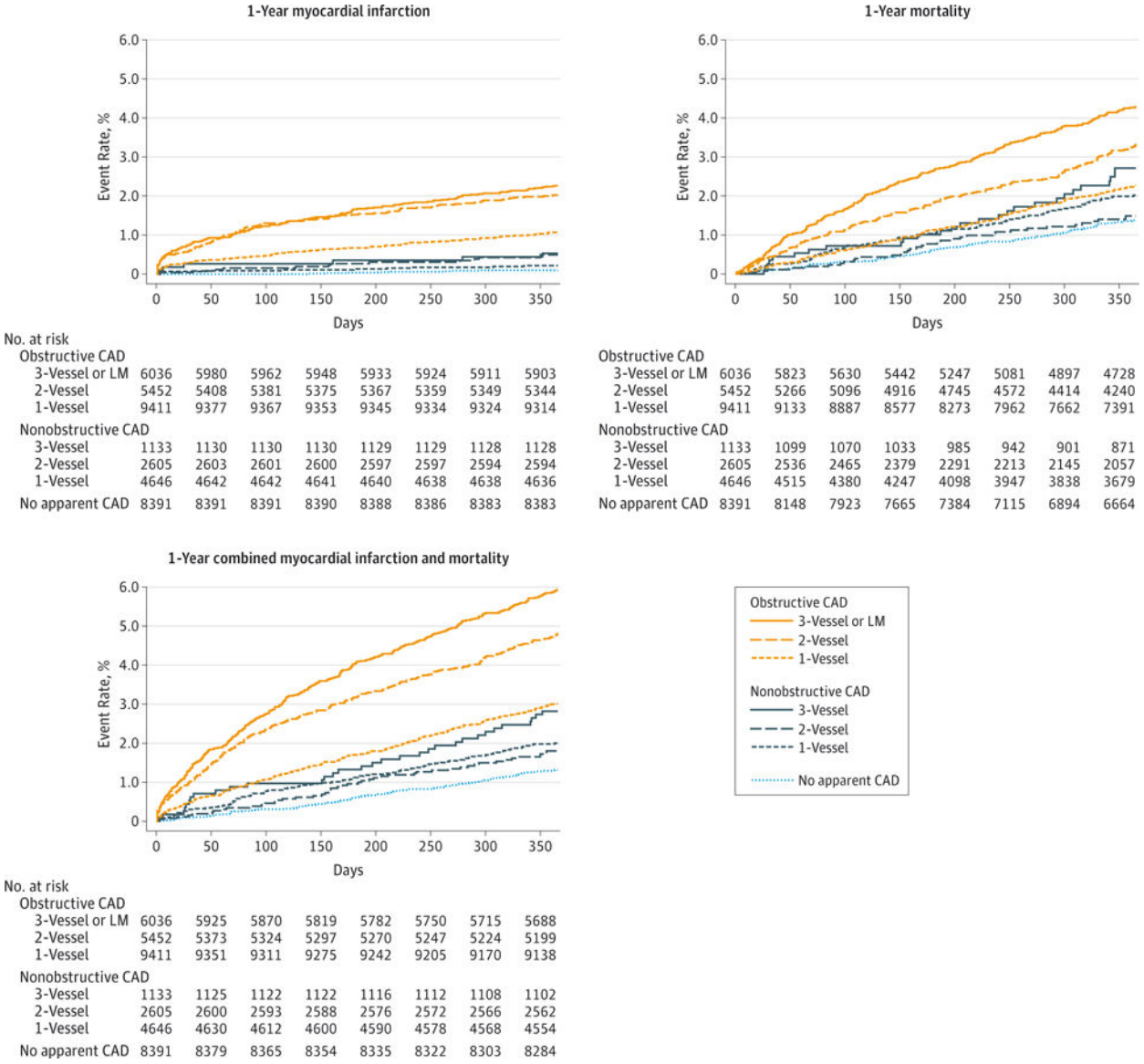
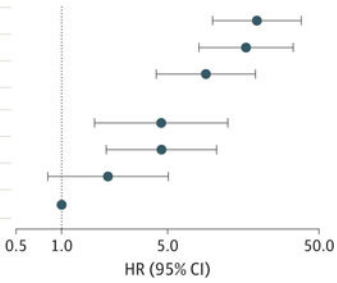



**Figure 1. Time-to-Event Plots for 1-Year Myocardial Infarction, Mortality, and Combined Myocardial Infarction and Mortality,by CAD Extent**

CAD indicates coronary artery disease; LM, left main.

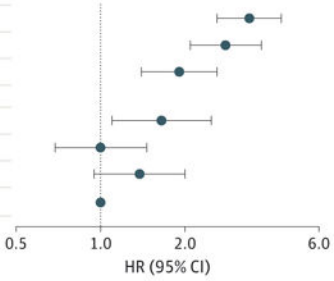
1-Year myocardial infarction

| | No. of Events | No. of Patients | HR (95% CI) |
|---|---|---|---|
| Obstructive CAD | | | |
| 3-Vessel or left main | 137 | 6036 | 19.5 (9.9-38.2) |
| 2-Vessel | 110 | 5452 | 16.5 (8.1-33.7) |
| 1-Vessel | 101 | 9411 | 9.0 (4.2-19.0) |
| Nonobstructive CAD | | | |
| 3-Vessel | 6 | 1133 | 4.5 (1.6-12.5) |
| 2-Vessel | 13 | 2605 | 4.6 (2.0-10.5) |
| 1-Vessel | 10 | 4646 | 2.0 (0.8-5.1) |
| No apparent CAD | 8 | 8391 | 1 [Reference] |




1-Year mortality

| | No. of Events | No. of Patients | HR (95% CI) |
|---|---|---|---|
| Obstructive CAD | | | |
| 3-Vessel or left main | 239 | 6036 | 3.4 (2.6-4.4) |
| 2-Vessel | 164 | 5452 | 2.8 (2.1-3.7) |
| 1-Vessel | 192 | 9411 | 1.9 (1.4-2.6) |
| Nonobstructive CAD | | | |
| 3-Vessel | 27 | 1133 | 1.6 (1.1-2.5) |
| 2-Vessel | 35 | 2605 | 1.0 (0.7-1.5) |
| 1-Vessel | 85 | 4646 | 1.4 (1.0-2.0) |
| No apparent CAD | 103 | 8391 | 1 [Reference] |




1-Year combined myocardial infarction and mortality

| | No. of Events | No. of Patients | HR (95% CI) |
|---|---|---|---|
| Obstructive CAD | | | |
| 3-Vessel or left main | 358 | 6036 | 4.5 (3.5-5.7) |
| 2-Vessel | 262 | 5452 | 3.8 (2.8-5.0) |
| 1-Vessel | 284 | 9411 | 2.4 (1.8-3.2) |
| Nonobstructive CAD | | | |
| 3-Vessel | 32 | 1133 | 1.8 (1.2-2.7) |
| 2-Vessel | 47 | 2605 | 1.2 (0.9-1.7) |
| 1-Vessel | 93 | 4646 | 1.4 (1.0-2.0) |
| No apparent CAD | 110 | 8391 | 1 [Reference] |

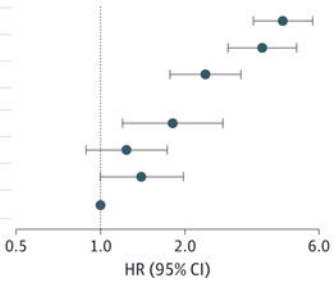



**Figure 2. Adjusted Cox Model Results for 1-Year Myocardial Infarction, Mortality, and Combined Myocardial Infarction and Mortality by CAD Extent, Relative to No Apparent CAD**

CAD indicates coronary artery disease; HR, hazard ratio.

**Table 1**

Patient Characteristics by No Apparent and Nonobstructive CAD

| | | Nonobstructive CAD, No. (%) | | | |
|---|---|---|---|---|---|
| | **No Apparent CAD, No. (%)** | **1-Vessel** | **2-Vessel** | **3-Vessel** | ***P* Value** |
| Patients, No. | 8391 | 4646 | 2605 | 1133 | |
| Age, median (IQR), y | 58.5 (51.3–63.3) | 61.9 (57.1–66) | 62.3 (57.6–66.7) | 63.0 (58.7–67.8) | <.001 |
| Male sex | 7456 (88.9) | 4401 (94.7) | 2505 (96.2) | 1103 (97.4) | <.001 |
| White race | 6055 (72.2) | 3731 (80.3) | 2115 (81.2) | 923 (81.5) | <.001 |
| Clinical comorbidities | | | | | |
| Hypertension | 6452 (76.9) | 3905 (84.1) | 2256 (86.6) | 1004 (88.6) | <.001 |
| Hyperlipidemia | 6200 (73.9) | 3801 (81.8) | 2212 (84.9) | 966 (85.3) | <.001 |
| Diabetes | 2721 (32.4) | 1854 (39.9) | 1149 (44.1) | 542 (47.8) | <.001 |
| Tobacco use (ever) | 4703 (56.0) | 2823 (60.8) | 1639 (62.9) | 720 (63.5) | <.001 |
| Obese | 3301 (39.3) | 1743 (37.5) | 990 (38.0) | 442 (39.0) | .19 |
| CHF | 674 (8.0) | 441 (9.5) | 274 (10.5) | 134 (11.8) | <.001 |
| COPD | 1567 (18.7) | 1047 (22.5) | 628 (24.1) | 295 (26.0) | <.001 |
| CVD | 647 (7.7) | 508 (10.9) | 302 (11.6) | 150 (13.2) | <.001 |
| PAD | 608 (7.2) | 513 (11.0) | 380 (14.6) | 204 (18.0) | <.001 |
| PTSD | 2155 (25.7) | 1033 (22.2) | 580 (22.3) | 258 (22.8) | <.001 |
| Depression | 3960 (47.2) | 1967 (42.3) | 1088 (41.8) | 464 (41.0) | <.001 |
| Sleep apnea | 2075 (24.7) | 1126 (24.2) | 631 (24.2) | 248 (21.9) | .22 |
| Chronic kidney disease | 697 (8.3) | 485 (10.4) | 287 (11.0) | 157 (13.9) | <.001 |
| Dialysis | 113 (1.3) | 59 (1.3) | 57 (2.2) | 26 (2.3) | .001 |
| Framingham risk score | | | | | |
| Low (10-y risk <10%) | 3657 (43.6) | 1234 (26.6) | 594 (22.8) | 254 (22.4) | <.001 |
| Medium (10-y risk 10%–20%) | 3920 (46.7) | 2624 (56.5) | 1442 (55.4) | 632 (55.8) | |
| High (10-y risk >20%) | 814 (9.7) | 788 (17.0) | 569 (21.8) | 247 (21.8) | |
| Angiography indication | | | | | |
| Chest pain | 5693 (67.8) | 3063 (65.9) | 1753 (67.3) | 714 (63.0) | <.001 |
| Positive functional study | 2317 (27.6) | 1318 (28.4) | 705 (27.1) | 346 (30.5) | |

| | | Nonobstructive CAD, No. (%) | | | |
|---|---|---|---|---|---|
| | No Apparent CAD, No. (%) | 1-Vessel | 2-Vessel | 3-Vessel | *P* Value |
| Ischemic heart disease | 100 (1.2) | 102 (2.2) | 57 (2.2) | 29 (2.6) | |
| Stable angina | 281 (3.3) | 163 (3.5) | 90 (3.5) | 44 (3.9) | |
| Postangiography cardiac medications | | | | | |
| Statins | 3758 (44.8) | 2745 (59.1) | 1641 (63.0) | 710 (62.7) | <.001 |
| β-Blockers | 3142 (37.4) | 2186 (47.1) | 1322 (50.7) | 577 (50.9) | <.001 |
| ACEIs/ARBs | 2848 (33.9) | 2071 (44.6) | 1188 (45.6) | 556 (49.1) | <.001 |
| Postangiography revascularization | | | | | |
| None | 8374 (99.8) | 4603 (99.1) | 2573 (98.8) | 1115 (98.4) | |
| CABG | 2 (<0.05) | 6 (0.1) | 3 (0.1) | 2 (0.2) | <.001 |
| PCI | 15 (0.2) | 37 (0.8) | 29 (1.1) | 16 (1.4) | |

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IQR, interquartile range; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PTSD, posttraumatic stress disorder.

## Table 2

Patient Characteristics by Obstructive CAD

| | Obstructive CAD, No. (%) | | | |
|---|---|---|---|---|
| | 1-Vessel | 2-Vessel | 3-Vessel or Left Main | *P* Value |
| Patients, No. | 9411 | 5452 | 6036 | |
| Age, median (IQR), y | 63.2 (59.3–67.8) | 64.0 (60.2–69.1) | 64.6 (60.9–70.8) | <.001 |
| Male sex | 9191 (97.7) | 5371 (98.5) | 5981 (99.1) | <.001 |
| White race | 8073 (85.8) | 4763 (87.4) | 5249 (87.0) | .01 |
| Clinical comorbidities | | | | |
| Hypertension | 8125 (86.3) | 4781 (87.7) | 5314 (88.0) | .004 |
| Hyperlipidemia | 8041 (85.4) | 4801 (88.1) | 5340 (88.5) | <.001 |
| Diabetes | 4026 (42.8) | 2553 (46.8) | 2854 (47.3) | <.001 |
| Tobacco use (ever) | 5781 (61.4) | 3243 (59.5) | 3583 (59.4) | .01 |
| Obese | 3189 (33.9) | 1773 (32.5) | 1820 (30.2) | <.001 |
| CHF | 948 (10.1) | 543 (10.0) | 566 (9.4) | .35 |
| COPD | 1943 (20.6) | 1020 (18.7) | 970 (16.1) | <.001 |
| CVD | 1250 (13.3) | 838 (15.4) | 1038 (17.2) | <.001 |
| PAD | 1569 (16.7) | 1126 (20.7) | 1351 (22.4) | <.001 |
| PTSD | 1777 (18.9) | 898 (16.5) | 863 (14.3) | <.001 |
| Depression | 3322 (35.3) | 1707 (31.3) | 1653 (27.4) | <.001 |
| Sleep apnea | 1823 (19.4) | 916 (16.8) | 855 (14.2) | <.001 |
| Chronic kidney disease | 1114 (11.8) | 756 (13.9) | 870 (14.4) | <.001 |
| Dialysis | 163 (1.7) | 115 (2.1) | 101 (1.7) | .16 |
| Framingham risk score | | | | |
| Low (10-y risk <10%) | 1734 (18.4) | 787 (14.4) | 776 (12.9) | <.001 |
| Medium (10-y risk 10%–20%) | 5397 (57.3) | 3099 (56.8) | 3242 (53.7) | |
| High (10-y risk >20%) | 2280 (24.2) | 1566 (28.7) | 2018 (33.4) | |
| Angiography indication | | | | |
| Chest pain | 5944 (63.2) | 3390 (62.2) | 3792 (62.8) | <.001 |
| Positive functional study | 2384 (25.3) | 1348 (24.7) | 1462 (24.2) | |
| Ischemic heart disease | 650 (6.9) | 452 (8.3) | 548 (9.1) | |
| Stable angina | 433 (4.6) | 262 (4.8) | 234 (3.9) | |
| Postangiography cardiac medications | | | | |
| Statins | 6992 (74.3) | 4083 (74.9) | 4410 (73.1) | .07 |
| β-Blockers | 6348 (67.5) | 3926 (72.0) | 4487 (74.3) | <.001 |
| ACEIs/ARBs | 4854 (51.6) | 2893 (53.1) | 2961 (49.1) | <.001 |
| Postangiography revascularization | | | | |
| None | 4628 (49.2) | 2274 (41.7) | 2408 (39.9) | <.001 |
| CABG | 323 (3.4) | 879 (16.1) | 2815 (46.6) | |
| PCI | 4460 (47.4) | 2299 (42.2) | 813 (13.5) | |

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IQR, interquartile range; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PTSD, posttraumatic stress disorder.

**Table 3**

Kaplan-Meier Estimates of 1-Year MI, All-Cause Mortality, and Combined Outcome Rates by CAD Extent

| | | Nonobstructive CAD, % (95% CI) | | | Obstructive CAD, % (95% CI) | | |
|---|---|---|---|---|---|---|---|
| | No Apparent CAD, % (95% CI) | 1-Vessel | 2-Vessel | 3-Vessel | 1-Vessel | 2-Vessel | 3-Vessel/Left Main |
| 1-Year MI | 0.11 (0.10–0.20) | 0.24 (0.10–0.40) | 0.56 (0.30–1.00) | 0.59 (0.30–1.30) | 1.18 (1.00–1.40) | 2.18 (1.80–2.60) | 2.47 (2.10–2.90) |
| 1-Year mortality | 1.38 (1.10–1.70) | 2.02 (1.60–2.50) | 1.50 (1.10–2.10) | 2.72 (1.90–3.90) | 2.25 (2.00–2.60) | 3.33 (2.90–3.90) | 4.30 (3.80–4.90) |
| 1-Year combined outcomes | 1.48 (1.20–1.80) | 2.18 (1.80–2.70) | 1.88 (1.40–2.50) | 3.18 (2.30–4.50) | 3.13 (2.80–3.50) | 4.94 (4.40–5.60) | 6.19 (5.60–6.90) |

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction.