Utilization of Secondary Prevention Therapies in Patients With Nonobstructive Coronary Artery Disease Identified During Cardiac Catheterization
Insights From the National Cardiovascular Data Registry
Cath-PCI Registry

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Background—Secondary prevention therapies are indicated for patients with coronary artery disease (CAD). However, patients with nonobstructive CAD may be less likely to receive these therapies compared with patients with obstructive CAD. Therefore, we compared rates of secondary prevention medication prescription between patients with nonobstructive and obstructive CAD.

Methods and Results—We conducted a retrospective cohort study of 1,489,745 CAD patients undergoing cardiac catheterization in 786 US centers between 2004 and 2007. We measured rates of aspirin, statin, β-blocker, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) prescription at hospital discharge among eligible patients; 237,167 (15.9%) patients had nonobstructive CAD and 1,252,578 (84.1%) had obstructive CAD. Compared with obstructive CAD patients, nonobstructive CAD patients had significantly lower rates of aspirin (72.7% versus 90.9%), statin (60.0% versus 80.3%), β-blocker (57.9% versus 79.4%), and ACEI/ARB (45.9% versus 58.6%; all probability values <0.0001) prescription at hospital discharge. After multivariable adjustment, nonobstructive CAD patients remained significantly less likely to receive prescriptions for aspirin (odds ratio, 0.37; 95% confidence interval, 0.35 to 0.39), statins (odds ratio, 0.45; 95% confidence interval, 0.43 to 0.48), β-blockers (odds ratio, 0.46; 95% CI, 0.44 to 0.47), or ACEI/ARBs (odds ratio, 0.83; 95% confidence interval, 0.80 to 0.86) compared with obstructive CAD patients. Secondary analyses of selected subgroups supported the primary findings.

Conclusions—Patients with nonobstructive CAD were significantly less likely to receive secondary prevention medication prescription at hospital discharge, as compared with patients with obstructive CAD. These findings highlight an opportunity to improve the quality of care for CAD patients with nonobstructive disease. (Circ Cardiovasc Qual Outcomes. 2010;3:632-641.)

Key Words: prevention ■ coronary disease ■ epidemiology

Secondary prevention therapies are indicated for patients with established coronary artery disease (CAD) and those at high risk for developing CAD to improve survival, reduce risk of future myocardial infarctions (MI), decrease the need for interventional procedures, and improve quality of life.1 These strategies, including secondary prevention medications (eg, aspirin, statins, β-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers [ARB]), have been codified into the 2006 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease.2 These guidelines reflect the current standard of care for patients with CAD.

Coronary angiography remains the criterion standard for the diagnosis of CAD and assessment of its severity. CAD severity is usually classified as obstructive or nonobstructive, depending on the presence or absence of flow-limiting atherosclerotic coronary plaques. Although this anatomic taxonomy assists in determining the role of these plaques in myocardial ischemia, it is less useful in predicting the future risk of plaque rupture and subsequent acute coronary syndrome. In fact, pathological and angiographic studies have demonstrated that a majority of MIs result from the rupture of
nonobstructive coronary plaques. Accordingly, indications for secondary prevention therapies are not contingent on the presence of obstructive or nonobstructive CAD at the time of coronary angiography. However, the focus on obstructive CAD at the time of coronary angiography may inadvertently lead to suboptimal secondary prevention treatment for patients with nonobstructive CAD. Currently, little is known about secondary prevention treatment patterns among these patients.

To address this gap in knowledge, we used the National Cardiovascular Data Registry (NCDR) Cath-PCI registry to evaluate secondary prevention medication prescription among patients with CAD after coronary angiography as a function of the degree of CAD obstruction. Specifically, we compared rates of aspirin, statin, β-blocker, and ACEI/ARB prescription at hospital discharge between patients with nonobstructive CAD and obstructive CAD. We hypothesized that patients with nonobstructive CAD would have significantly lower rates of secondary prevention medication prescription compared with patients with obstructive CAD. Demonstration of differences in secondary prevention among these CAD patients could lead to interventions to improve the quality of CAD prevention care and improved patient outcomes.

WHAT IS KNOWN

• Secondary prevention therapies are indicated for patients with coronary artery disease (CAD), which is typically defined by the presence of obstructive atherosclerotic plaques.

• However, patients with nonobstructive CAD may also benefit from secondary prevention therapies.

WHAT THE STUDY ADDS

• Patients with nonobstructive CAD were significantly less likely to receive secondary prevention medication prescription at hospital discharge, as compared with patients with obstructive CAD.

• Similar gaps occurred among patients with nonobstructive CAD who had class I indications for secondary prevention medications.

• These findings highlight an opportunity to improve the quality of care for CAD patients with nonobstructive disease.

Methods

Data Collection

The NCDR Cath-PCI Registry, cosponsored by the ACC and Society for Coronary Angiography and Intervention, is a national registry of patients undergoing diagnostic cardiac catheterizations and/or percutaneous coronary intervention (PCI) in the United States. Patient and procedural information are collected using a standardized set of data elements and definitions, systematic data entry and transmission procedures, and rigorous data quality assurance standards. Only institutions with submissions passing the inclusion/exclusion criteria for data completeness were included. Additionally, a national external audit program, conducted by the West Virginia Medical Institute and sponsored by the NCDR, reviews and verifies data from a random sample of sites. The complete definitions of all variables, along with audit and quality control procedures, were prospectively defined by a committee of the ACC and are available at the ACC website (https://www.ncdr.com/WebNCDR/DefaultCathPCI.aspx).

Our study used data from Version 3.0 of the Cath-PCI Registry.

Study Population

We analyzed 2,479,874 cardiac catheterizations submitted to the NCDR Cath-PCI registry from 801 institutions between January 1, 2004, and December 31, 2007 (Figure 1). From these data, we excluded those patients undergoing PCI procedures without an immediately preceding diagnostic cardiac catheterization (eg, those receiving a "staged" PCI procedure) (n=256,718, 10.4%), patients with repeat diagnostic cardiac catheterizations occurring during the same hospital admission (n=24,317, 1.0%), patients who were discharged to hospice care or receiving comfort care only (n=28,008, 1.1%), patients with missing discharge medication information (n=253,739, 10.2%), patients with nonobstructive CAD receiving PCI (n=17,402, 0.7%), patients with normal coronary arteries, defined as no luminal stenosis >20% (n=408,359, 16.5%), and patients who died during the index hospitalization (n=1,586, 0.1%). Our final study cohort included 1,489,745 patients who underwent cardiac catheterization at 786 institutions.

Data Definitions

Consistent with standard definitions of flow-limiting stenoses, nonobstructive CAD was defined as a coronary artery stenosis >20% but <50% in the left main coronary artery or >20% but <70% in any other coronary artery, as recorded in the catheterization report. Obstructive CAD was defined as any stenosis ≥50% in the left main coronary artery and/or ≥70% in any other coronary artery. Patients with a history of PCI were classified as having either nonobstructive or obstructive CAD, depending on the degree of stenosis noted on the current catheterization report (eg, in-stent restenosis <70% would be defined as nonobstructive). Patients with prior coronary artery bypass grafting, regardless of the degree of CAD noted on the index catheterization, were classified as having obstructive CAD. To determine whether a graded relationship between degree of CAD obstruction and rates of medication prescription existed, we further stratified CAD patients into mild (left main stenosis ≤20% and all other stenoses >20% but ≤50%) and moderate (left main stenosis >20% but <50% and/or any other stenosis >50% but <70%) disease, based on prior classifications of CAD severity.

Prescription rates for aspirin, statin, β-blocker, and ACEI/ARB at hospital discharge were collected from the discharge reports. Patients with a documented contraindication or missing data for 1 or more of the medications were excluded only from the analysis or analyses that evaluated that particular medication or medications (contraindicated or missing aspirin, 72,029 [4.8%] patients; contraindicated or missing statin, 67,903 [4.6%] patients; contraindicated or missing β-blocker, 75,845 [5.1%] patients; contraindicated or missing ACEI/ARB, 82,500 [5.5%] patients) (Figure 1).

Statistical Analysis

After classifying patients by the presence of nonobstructive or obstructive CAD, we compared demographics, clinical history, in-hospital medications, admission presentation, in-hospital adverse outcomes, and hospital characteristics by patient group. Categorical variables were compared using the Pearson χ² test, and continuous variables were compared using Wilcoxon tests.

For our primary analysis, we used generalized estimating equation (GEE) models to compare prescription rates of each secondary prevention medication (aspirin, statin, β-blocker, and ACEI/ARB) between patients with nonobstructive and obstructive CAD. GEE models were used to adjust for the clustering of patients by medical center. On the basis of a priori clinical reasoning and prior studies, we then entered potential confounders of the relationship between coronary artery stenosis severity and secondary prevention medication prescription into our models. Selected factors included demographics (age, sex, race [white versus nonwhite], insurance
payor (commercial, government, or other)); clinical history (body mass index, prior MI, prior PCI, prior coronary artery bypass grafting, prior congestive heart failure [CHF], ejection fraction, hypertension, diabetes, glomerular filtration rate [GFR], cerebrovascular disease, peripheral vascular disease, chronic lung disease, tobacco use, dyslipidemia); in-hospital medications (aspirin, clopidogrel, β-blocker, statin); admission presentation (symptoms, ACS on admission, CHF on admission, cardiogenic shock on admission); periprocedural adverse outcomes (MI, cardiogenic shock, CHF, cerebrovascular accident, bleeding, vascular complications); and hospital characteristics (hospital location, profit status, teaching/nonteaching hospital, geographic region, and PCI volume). All of these confounders were entered into all of the models constructed for our analyses. Rates of missing data were <1% for all variables except ejection fraction (16%) and GFR (5.2%). Missing ejection fraction values were imputed to a group median value based on the presence of ST-elevation–MI (STEMI), CHF, cardiogenic shock, and prior MI. Missing GFR values were imputed to a group median value based on the presence of STEMI, sex, and renal failure. Variables used to assign groups for imputation were derived from the NCDR mortality models (currently under review; http://www.ncdr.com/WebNCDR/RESEARCH.ASPX).

To further support our primary findings, we also conducted several secondary analyses. First, to determine whether secondary prevention medication prescription was a function of increasing CAD obstruction (ie, a "dose-response relationship"), we stratified the nonobstructive CAD population into mildly and moderately nonobstructive CAD populations. We then conducted secondary analyses comparing prescription rates among mildly nonobstructive, moderately nonobstructive, and obstructive CAD patients.

Second, to determine whether differences in prescription rates were present among those patients with clear indications for each medication class, we restricted our cohort to those patients with class I guideline indications for each medication.2,18 For aspirin use, we examined all patients with an acute coronary syndrome (ACS) presentation and patients with prior CAD or a CAD risk equivalent (prior MI, prior revascularization, cerebrovascular disease, peripheral vascular disease, or diabetes); for statins, we examined those patients undergoing catheterization for unstable angina or non-STEMI (based on the fact that this population is the only population that has current guideline recommendations specifically for statins18); for β-blockers, we examined those patients undergoing catheterization for ACS, with a history of MI, or with an ejection fraction <40%; for ACEI/ARB, we examined those patients with a history of diabetes, hypertension, chronic kidney disease (GFR <60 mL/min), or an ejection fraction <40%. Among these subgroups, we compared rates of secondary prevention medication prescription by nonobstructive and obstructive CAD.

Third, to determine whether differences in prescription rates were present among higher-risk CAD patients, we identified 2 patient subgroups at particularly high risk for adverse cardiac events: patients hospitalized with an ACS and patients with prior CAD or a CAD risk equivalent (prior MI, prior revascularization, cerebrovascular disease, peripheral vascular disease, or diabetes).1 We added first-order interaction terms (ACS*CAD severity; prior CAD or CAD risk equivalent*CAD severity) into our primary model to test for effect modification among these subgroups and then stratified by these comorbidities to compare rates of secondary prevention medication prescription by nonobstructive and obstructive CAD.

Figure 1. Study cohort creation.
Table 1. Patient Characteristics by Nonobstructive and Obstructive CAD

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Nonobstructive CAD (n=237 167)</th>
<th>Obstructive CAD (n=1 252 578)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th, 75th percentiles), y</td>
<td>64 (55, 73)</td>
<td>65 (56, 74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>124 316 (52.4)</td>
<td>842 928 (67.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>198 531 (83.7)</td>
<td>1 074 220 (85.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insurance status, n (%)</td>
<td>32920 (1.4)</td>
<td>294 351 (23.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30), n (%)</td>
<td>107 285 (45.2)</td>
<td>517 768 (41.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>44 348 (18.7)</td>
<td>361 008 (28.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>70 039 (29.5)</td>
<td>419 078 (33.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>60 (50, 65)</td>
<td>55 (45, 60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CHF, n (%)</td>
<td>25 505 (10.8)</td>
<td>148 527 (11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF, median (25th, 75th percentiles), %</td>
<td>60 (50, 65)</td>
<td>55 (45, 60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>179 390 (75.6)</td>
<td>966 347 (77.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>69 089 (29.1)</td>
<td>426 664 (34.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR, median (25th, 75th percentiles), mL/min</td>
<td>74 (59, 89)</td>
<td>71 (57, 87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>176 965 (75.6)</td>
<td>1 079 764 (87.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>59 305 (25.1)</td>
<td>737 418 (59.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>69 089 (29.1)</td>
<td>426 664 (34.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>114 153 (48.4)</td>
<td>70 957 (56.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>108 122 (45.6)</td>
<td>427 042 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class 2</td>
<td>60 868 (25.7)</td>
<td>275 306 (22.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class 3</td>
<td>45 197 (19.1)</td>
<td>325 170 (26.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class 4</td>
<td>16 663 (7.0)</td>
<td>214 849 (17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>94 (0.4)</td>
<td>9718 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiogenic shock, n (%)</td>
<td>112 (0.5)</td>
<td>5650 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>168 (0.8)</td>
<td>7491 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>194 (0.8)</td>
<td>3788 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding, n (%)</td>
<td>1183 (0.5)</td>
<td>25 036 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular complications, n (%)</td>
<td>529 (0.2)</td>
<td>8125 (0.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Continued)
For all secondary analyses, GEE models were used similar to the primary analysis. All analyses were conducted with SAS software version 9.1 (SAS Institute, Cary, NC). Institutional review board approval for the analyses of the Cath-PCI registry was obtained by the Duke Clinical Research Institute.

Results

Patient Characteristics

Of the 1,489,745 CAD patients in our study cohort, 237,167 (15.9%) had nonobstructive CAD and 1,252,578 (84.1%) had obstructive CAD. Patient characteristics are shown in Table 1. In general, patients with nonobstructive CAD were more likely to be younger, female, nonwhite, have lower rates of prior cardiac and vascular disease, have no or atypical symptoms on admission, and have fewer in-hospital adverse outcomes as compared with those with obstructive CAD. In addition, nonobstructive CAD patients had lower rates of inpatient medication use (ASA, clopidogrel, β-blockers, and statins) than obstructive CAD patients. Higher rates of inpatient medication use were present among patients with ACS compared with patients without ACS, regardless of the presence of obstructive or nonobstructive CAD (Table 2). Nonetheless, obstructive CAD patients with ACS had higher rates of medication use compared with nonobstructive CAD patients.

Rates of Secondary Prevention Medication Prescription Between Nonobstructive and Obstructive CAD Patients

Nonobstructive CAD patients had significantly lower rates of aspirin (72.7% versus 90.9%), statin (60.0% versus 80.3%), β-blocker (57.9% versus 79.4%), and ACEI/ARB (45.9% versus 58.6%; all probability values <0.0001) prescription at hospital discharge, as compared with obstructive CAD patients. After adjustment for demographic, clinical, inpatient, and hospital factors, nonobstructive CAD patients remained significantly less likely to receive prescriptions for all 4 medications, as compared with obstructive CAD patients (Figure 2).

Rates of Secondary Prevention Medication Prescription Between Mildly Nonobstructive, Moderately Nonobstructive, and Obstructive CAD Patients

Of the 237,167 patients with nonobstructive CAD, 181,837 (76.7%) had mildly nonobstructive CAD and 55,330 (23.3%) had moderately nonobstructive CAD. In unadjusted analysis, both mildly and moderately nonobstructive CAD patients had significantly lower rates of rates of aspirin, statin, β-blocker, and ACEI/ARB prescription, as compared with obstructive CAD patients (Figure 3; pairwise comparison probability values <0.0001). Furthermore, prescription rates decreased
in a stepwise fashion with decreasing severity of obstructive disease. Mildly nonobstructive CAD patients had, on average, between 3.3% and 7.2% lower rates of secondary prevention medication prescription than moderately nonobstructive CAD patients.

After adjustment for demographic, clinical, inpatient, and hospital factors, the interaction term for increasing CAD obstruction for all 4 secondary prevention medication classes was significant (probability value <0.0001), indicating that the likelihood of receiving medication prescriptions significantly increased with increasing levels of CAD severity in a dose-response relationship. Both mildly and moderately nonobstructive CAD patients remained significantly less likely to receive prescriptions for all 4 medications as compared with obstructive CAD patients (Figure 2).

### Rates of Secondary Prevention Medication Prescription Among CAD Patients With Class I Indications

For each of the 4 medication classes of interest, patients with class I indications for their use were identified. Among the 460 057 patients with class I indications for aspirin, 41 050 (8.9%) had nonobstructive CAD and 419 007 (91.1%) had obstructive CAD. Among the 672 155 patients with class I

### Table 2. Inpatient Medication Use by Nonobstructive CAD and Obstructive CAD, Stratified by ACS and Non-ACS Presentation

<table>
<thead>
<tr>
<th></th>
<th>Total (n=1 489 745)</th>
<th>Nonobstructive CAD (n=237 167)</th>
<th>Obstructive CAD (n=1 252 578)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACS presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>730 779 (89.7)</td>
<td>64 949 (83.2)</td>
<td>665 830 (90.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>502 520 (61.4)</td>
<td>26 443 (33.6)</td>
<td>476 077 (64.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>579 869 (71.9)</td>
<td>49 463 (63.3)</td>
<td>530 406 (72.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>447 375 (54.8)</td>
<td>40 668 (51.8)</td>
<td>406 707 (55.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Non-ACS presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>525 950 (79.8)</td>
<td>112 016 (71.9)</td>
<td>413 934 (82.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>294 203 (44.3)</td>
<td>32 862 (20.9)</td>
<td>261 341 (51.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>382 957 (58.0)</td>
<td>79 307 (50.5)</td>
<td>303 650 (60.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>367 735 (55.6)</td>
<td>73 485 (46.7)</td>
<td>294 250 (58.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ASA indicates aspirin.

**Aspirin**

Non-obstructive CAD vs. Obstructive CAD

- Mildly non-obstructive CAD vs. Obstructive CAD: 0.37 (0.35, 0.39)
- Moderately non-obstructive CAD vs. Obstructive CAD: 0.35 (0.33, 0.37)

Statin

Non-obstructive CAD vs. Obstructive CAD

- Mildly non-obstructive CAD vs. Obstructive CAD: 0.43 (0.4, 0.45)
- Moderately non-obstructive CAD vs. Obstructive CAD: 0.55 (0.52, 0.59)

Beta-blockers

Non-obstructive CAD vs. Obstructive CAD

- Mildly non-obstructive CAD vs. Obstructive CAD: 0.46 (0.44, 0.47)
- Moderately non-obstructive CAD vs. Obstructive CAD: 0.57 (0.55, 0.6)

ACEI/ARB

Non-obstructive CAD vs. Obstructive CAD

- Mildly non-obstructive CAD vs. Obstructive CAD: 0.83 (0.8, 0.86)
- Moderately non-obstructive CAD vs. Obstructive CAD: 0.82 (0.79, 0.85)

Figure 2. Adjusted odds ratios with 95% confidence intervals of receipt of secondary prevention medication prescription at hospital discharge among patients with nonobstructive CAD (n=237 167), mildly nonobstructive CAD (n=181 137), and moderately nonobstructive CAD (n=55 330), all in comparison to obstructive CAD (n=1 252 578).
indications for statins, 75,914 (11.3%) had nonobstructive CAD and 596,241 (88.7%) had obstructive CAD. Among the 1,021,079 patients with class I indications for β-blockers, 114,892 (11.3%) had nonobstructive CAD and 906,187 (88.7%) had obstructive CAD. Among the 1,319,357 patients with class I indications for ACEI/ARBs, 209,003 (15.8%) had nonobstructive CAD and 1,110,354 (84.2%) had obstructive CAD.

Among these subgroups with class I indications, nonobstructive CAD patients had significantly lower unadjusted rates of aspirin (80.6% versus 92.9%), statin (64.9% versus 82.1%), β-blocker (66.0% versus 83.1%), and ACEI/ARB (49.6% versus 60.6%) prescription at discharge, as compared with obstructive CAD patients. After adjustment for demographic, clinical, inpatient, and hospital factors, nonobstructive CAD patients remained significantly less likely to receive prescriptions for all 4 medications as compared with obstructive CAD patients (Figure 4).

Rates of Secondary Prevention Medication Prescription Among CAD Patients With Prior CAD or a CAD Equivalent
A total of 866,286 (58.2%) of patients in our study cohort had either prior CAD or a CAD risk equivalent. Of these, 119,225 (13.8%) had nonobstructive CAD and 747,061 (86.2%) had obstructive CAD. At hospital discharge, nonobstructive CAD patients had significantly lower rates of aspirin (75.3% versus 90.4%), statin (65.8% versus 80.2%), β-blocker (62.8% versus 79.9%), and ACEI/ARB (52.9% versus 62.2%) prescription as compared with obstructive CAD patients.

After multivariable adjustment, the interaction term for prior CAD or a CAD risk equivalent (prior CAD or CAD risk equivalent*CAD severity) for all 4 secondary prevention medication classes was significant (probability value <0.0001), indicating that prior CAD or a CAD risk equivalent modified secondary prevention prescription rates between nonobstructive and obstructive CAD. Nonobstructive CAD patients remained significantly less likely to receive prescriptions for all 4 medications as compared with obstructive CAD patients (Figure 5).

Discussion
In this large study of patients undergoing coronary angiography, we found that the presence of nonobstructive CAD was significantly and strongly associated with lower rates of

Figure 4. Adjusted odds ratios with 95% confidence intervals of receipt of secondary prevention medication prescription at hospital discharge between nonobstructive and obstructive CAD patients with class I indications for each medication.
secondary prevention medication prescription at hospital discharge compared with patients with obstructive CAD. Prescription rates exhibited a dose-response relationship with CAD severity, with the lowest rates of medication prescription occurring in patients with mildly nonobstructive CAD, followed by those with moderately nonobstructive CAD, then those with obstructive CAD. Furthermore, higher-risk nonobstructive CAD patients with clear indications and proven benefits from these therapies—ie, those with class I indications for 1 or more secondary prevention medications, undergoing catheterization for ACS, or having prior CAD or a CAD risk equivalent—also had lower rates of medication prescription as compared with obstructive CAD patients. These findings provide, to our knowledge, the first description of secondary prevention medication prescription among nonobstructive CAD patients and demonstrate significant gaps in its provision.

Few studies have examined patients with nonobstructive CAD, and almost all of these have focused on ACS populations.14–17 For example, Roe et al17 demonstrated that nonobstructive CAD patients had a combined death and reinfarction rate of 6.0% 30 days after NSTEMI. Similarly, Bugiardini et al15 demonstrated that nonobstructive CAD patients had a combined death and reinfarction rate of 2.1% 1 year after non-STEMI, based on pooled data from the TIMI-11B, 16, and 22 trials. These studies indicate rates of adverse events among nonobstructive CAD patients after ACS, though not as high as those with obstructive CAD, are not clinically insignificant. However, these studies did not evaluate secondary prevention medication use among the nonobstructive CAD patient population. Our study, by examining a large, national population of nonobstructive CAD patients, provides the most comprehensive assessment to date of the treatment patterns in this population and demonstrates both substantial gaps and potential opportunities in optimizing their cardiac care.

By characterizing gaps in secondary prevention medication prescription among nonobstructive CAD patients, our study identifies important targets for immediate improvement and suggests future directions for research. First, among those nonobstructive CAD patients with class I indications for secondary prevention medications, ACS, or prior CAD/CAD risk equivalents, aspirin, statins, β-blockers, and ACEI/ARBs have been shown to significantly reduce cardiac events.2,19 Interventions to optimize secondary prevention medication prescription at hospital discharge, such as discharge “checklists” or other systematic prescription programs, may help close this gap. In addition, these interventions may also need to focus on inpatient medication provision for patients with nonobstructive CAD, given that we also demonstrated gaps in their use compared with obstructive CAD patients. Second, a reevaluation of providers’ approach to secondary prevention

Figure 5. Adjusted ODDS RATIOS with 95% confidence intervals of receipt of secondary prevention medication prescription at hospital discharge between nonobstructive (n=79,094) and obstructive (n=1,252,578) CAD patients with ACS.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.32 (0.3, 0.34)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.42 (0.4, 0.45)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0.45 (0.41, 0.49)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>0.81 (0.78, 0.85)</td>
</tr>
</tbody>
</table>

Figure 6. Adjusted odds ratios with 95% confidence intervals of receipt of secondary prevention medication prescription at hospital discharge among nonobstructive (n=142,119) and obstructive (n=1,252,578) CAD patients with prior CAD or a CAD risk equivalent.
provision among patients with nonobstructive CAD may be necessary. In some cases, the message communicated from the catheterization laboratory to primary care providers and patients may be that the lack of obstructive CAD indicates “no significant disease,” which may inadvertently imply that preventive therapies are unnecessary. If this message then leads to reduced rates of secondary prevention therapies, especially among those with a clear indication for its use, then improvements in communication of a patient’s global cardiac risk and the role for appropriate secondary prevention treatments are necessary. Therefore, research into the role of communication among providers and patients on subsequent secondary prevention practices is needed. Finally, there are no current studies exploring the effect of secondary prevention medications on outcomes among nonobstructive CAD patients without class I indications for these therapies. The presence of atherosclerosis, regardless of its degree of obstruction, represents developing coronary disease and may confer significant risk for cardiac events for nonobstructive CAD patients over longer periods of time. Accordingly, institution of aggressive risk factor modification and other preventive therapies among these patients may significantly moderate this risk over time. This hypothesis has not been directly explored, and studies are needed to quantify potential benefits that these medications may have for patients with nonobstructive CAD.

Our analysis has several potential limitations. First, participation in the Cath-PCI registry of the NCDR is voluntary. However, our study cohort is composed of patients from 786 facilities throughout the United States, and there is no a priori reason to assume that care for nonobstructive CAD versus obstructive CAD patients would be different at hospitals that do not participate in NCDR. Second, obstructive and nonobstructive coronary disease was not verified by a core angiographic laboratory or other standardized methods of lesion assessment, such as quantitative coronary angiography. Accordingly, the potential for misclassification exists. However, the graded relationship demonstrated between CAD severity and medication prescription argues against significant misclassification. Furthermore, we have no reason to expect misclassification to be differential, suggesting that any bias would move our findings toward the null hypothesis. Third, incomplete documentation of contraindication to secondary prevention medications could also lead to misclassification. However, this misclassification probably would be nondifferential and again bias our results toward the null. Fourth, approximately 10% of patients were excluded from our study cohort because of missing discharge medication data, which could have introduced bias into our findings. However, the rates of nonobstructive CAD in these excluded patients was higher than in our study cohort (56% versus 16%), so we would expect that inclusion of these patients in our cohort would, if anything, accentuate the gaps in prescription between nonobstructive and obstructive CAD patients. Fifth, debate exists about optimal secondary prevention therapies for diabetic patients without prior CAD. However, because only 3497 (1.5%) of nonobstructive CAD patients in our cohort met this criteria, we would not expect it to materially affect our findings. Sixth, the NCDR cannot provide insight into postdischarge actions, such as prescription of secondary prevention medications during a subsequent outpatient visit. However, prior studies have demonstrated that if secondary prevention medications are not started during the hospitalization period, then they are less likely to be started in the outpatient period. Nonetheless, this study cannot directly measure whether these gaps in medication prescription persist after hospital discharge. Finally, the observed relationship between CAD severity and secondary prevention medication prescription may be confounded by unmeasured variables. This is a limitation of all observational studies. However, by adjusting for a large number of measured variables available through the NCDR registry, we believe that we can account for a significant amount of potential confounding.

In conclusion, this study found that the presence of nonobstructive CAD, in comparison to obstructive CAD, was significantly and strongly associated with lower rates of secondary prevention medication prescription at hospital discharge, both in the overall cohort as well as specified higher-risk CAD subgroups. These findings highlight both significant gaps and potential opportunities to improve the quality of care and outcomes for patients with nonobstructive CAD.

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Disclosures
None.

References


Utilization of Secondary Prevention Therapies in Patients With Nonobstructive Coronary Artery Disease Identified During Cardiac Catheterization: Insights From the National Cardiovascular Data Registry Cath-PCI Registry

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