Use of Preventive Medications in Patients With Nonobstructive Coronary Artery Disease: Analysis of the PROMISE Trial

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ABSTRACT

Background: Nonobstructive coronary artery disease (NOCAD) is commonly found on coronary computed tomography angiography (CCTA) during evaluation for coronary artery disease (CAD). There are no guidelines for the medical management of NOCAD, and practice is variable. We aimed to compare patterns of preventive medication use and continuation after identifying NOCAD vs normal coronaries or obstructive CAD on CCTA.

Methods: We analyzed data from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial dataset, comparing this combination of preventive medications vs usual care in women with ischemia with no obstructive disease—a statin-indicated condition. There are no analogous NOCAD-specific recommendations for other preventive medications, such as acetylsalicylic acid or renin–angiotensin system (RAS) blockers; however, a recent White Paper on ischemia with no obstructive disease—which encompasses patients with NOCAD and normal coronaries—and previous reviews, have generally recommended the combination of a statin, acetylsalicylic acid, and an RAS blocker for prevention of cardiovascular events in this population. Additionally, the use of angiotensin-converting enzyme inhibitors and statins, particularly in combination, can relieve symptoms of ischemia and improve quality of life in these patients. The ongoing Women’s Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) is a randomized trial comparing this combination of preventive medications vs usual care in women with ischemia with no obstructive disease (NCT03417388). Patients with NOCAD identified by invasive coronary artery angiography have historically been

Coronary computed tomography angiography (CCTA) has emerged as a common noninvasive modality to investigate patients presenting with symptoms suggestive of ischemic heart disease that may be caused by coronary artery disease (CAD). Traditionally, noninvasive CAD testing has focused on identifying patients with obstructive CAD, defined anatomically as coronary artery stenosis ≥ 50%-70% on invasive coronary angiography. However, in the current era, only 15%-55% of patients with chest pain who undergo CCTA or invasive angiography are found to have obstructive CAD, and up to 42% have nonobstructive coronary artery disease (NOCAD; epicardial plaque with stenosis 1%-69%). Although NOCAD was previously felt to portend a good prognosis and is often reported as “minimal/mild” or “moderate” CAD, several studies have demonstrated that patients with NOCAD have an increased risk of major adverse coronary events (MACE) compared to patients with no coronary artery stenosis or plaque. Furthermore, the risk of MACE rises with the extent of NOCAD, and patients with NOCAD in all 3 major coronary arteries have a risk of MACE similar to that of patients with single-vessel obstructive CAD.

There are presently no guidelines that focus on the management of patients with NOCAD, and evidence assessing the effectiveness of medications in this population is sparse. The 2016 Canadian Cardiovascular Society dyslipidemia guidelines consider the presence of clinical atherosclerosis, which includes coronary artery stenosis > 10%, to be a statin-indicated condition. There are no analogous NOCAD-specific recommendations for other preventive medications, such as acetylsalicylic acid or renin–angiotensin system (RAS) blockers; however, a recent White Paper on ischemia with no obstructive disease—which encompasses patients with NOCAD and normal coronaries—and previous reviews, have generally recommended the combination of a statin, acetylsalicylic acid, and an RAS blocker for prevention of cardiovascular events in this population. Additionally, the use of angiotensin-converting enzyme inhibitors and statins, particularly in combination, can relieve symptoms of ischemia and improve quality of life in these patients. The ongoing Women’s Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) is a randomized trial comparing this combination of preventive medications vs usual care in women with ischemia with no obstructive disease (NCT03417388). Patients with NOCAD identified by invasive coronary artery angiography have historically been

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restricted to patients with ≥2 follow-up visits after CCTA. We categorized patients as having either obstructive CAD, NOCAD, or normal coronaries. The primary outcome was the proportion of patients reporting continued use of combination preventive medications, defined as a statin, an antithrombotic, and a renin–angiotensin system blocker throughout follow-up after CCTA. Secondary outcomes included the proportion of visits reporting combination therapy and individual medications.

**Results:** We included 4388 patients, with a mean follow-up of 2.3 years. Most patients had NOCAD (48.6%), with normal coronaries in 38.9%, and obstructive CAD in 10.1%. Among NOCAD patients, the mean age was 61 years, and 47.2% were women. A total of 9.1% of NOCAD patients continued combination therapy, vs 12.4% with obstructive CAD, and 3.3% with normal coronaries (P < 0.001), primarily due to lower use of statins and antithrombotic agents. Similarly, patients with obstructive CAD, NOCAD, and normal coronaries reported using combination therapy during a mean of 35%, 24%, and 9% of visits, respectively (P < 0.001).

**Conclusions:** Few patients with NOCAD identified by CCTA used or continued combination preventive cardiovascular medications. Patients with NOCAD represent an at-risk population with potential for optimization of preventive medications.

The increased identification of patients with NOCAD as use of CCTA rises may allow for earlier implementation of preventive medications to mitigate MACE risk. Recent results from the Scottish Computed Tomography of the Heart (SCOT-HEART) trial showed that use of CCTA in patients with stable chest pain reduced the risk of MACE at 5 years, which has been attributed to increased initiation of preventive medications, mainly antiplatelets and statins, among patients with NOCAD identified on CCTA. Fewer than 60% of patients with obstructive CAD adhere to their cardiovascular medications, and the percentage may be even lower in patients with NOCAD who may be dissuaded from taking medications by the messaging they receive that they have “minimal” or “mild” disease. To date, no study has explored medication continuation in patients with NOCAD.

The objective of this study was to compare patterns of preventive medication use and continuation among patients with NOCAD compared to patients with obstructive CAD or normal coronaries identified on CCTA in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. We hypothesized that patients with NOCAD would be less likely to receive continued combination preventive therapy than patients with obstructive CAD, and more likely to receive the combination vs patients with normal coronaries identified on CCTA.

**Methods**

**Research design**

We conducted a cohort analysis of data from the PROMISE trial focused on patients who underwent CCTA.

**Data source**

The full anonymized database of the PROMISE trial was provided following a request through the National Heart, Lung and Blood Institute Data Repository via the BioLINCC website. BioLINCC is a repository of anonymized datasets of clinical trials and epidemiologic studies supported by the institute, including the PROMISE trial. The study design, full eligibility criteria, and primary results of the PROMISE trial have been published previously. Briefly, the PROMISE study was an open-label randomized controlled trial that compared the risk of downstream MACE and procedural complications in 10,053 patients with a low-to-intermediate likelihood of CAD randomized to CCTA vs functional testing after presenting with chest pain or equivalent symptoms.

**Cohort derivation**

We included all patients randomized to CCTA who successfully underwent CCTA, and attended ≥ 2 follow-up visits, including one visit at day 60 or month 6 (to identify short-term and longer-term changes in medication use after review of CCTA results).
Definitions of coronary status

We classified patients into 3 groups based on the presence of obstructive CAD, NOCAD, or normal coronaries as determined by CCTA. Obstructive CAD was defined as stenosis $\geq 50\%$ of the left main coronary artery, or $\geq 70\%$ in any other epicardial artery, as defined in the original PROMISE trial protocol. Nonobstructive CAD was defined as no obstructive CAD in any epicardial artery, plus either 1% to 49% stenosis in the left main coronary artery or 1% to 69% stenosis in the left anterior descending, left circumflex, or right coronary artery. We further separated patients as having “minimal” to “mild” NOCAD (Coronary Artery Disease-Reporting and Data System category 1 or 2; 1%-49% stenosis) or “moderate stenosis” (category 3; 50%-69% stenosis).\textsuperscript{22} We defined normal coronaries as either the absence of obstructive or nonobstructive stenosis or plaque in all 3 major epicardial arteries.

Definitions of exposure to preventive cardiovascular medications and outcomes

We assessed exposure to 3 categories of preventive cardiovascular medications from the post-randomization day-60 or month-6 visit (post-CCTA baseline) to the end of study follow-up, including: (i) antithrombotic agents (aspirin, clopidogrel, or oral anticoagulant if otherwise indicated); (ii) statins; (iii) RAS blockers (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Additionally, we assessed exposure to $\beta$-blockers.

The primary outcome was the proportion of patients with continued combination preventive medications, defined as continuous use without interruption of an antithrombotic, statin, and RAS blocker from first post-CCTA visit (day 60 or month 6 after randomization) until last follow-up. Secondary outcomes included the proportion of visits with use of combination preventive medications; continued use and proportion of visits with use of each medication category; and use of each medication category at each follow-up visit.

Data extraction

Data for each study participant were extracted from the PROMISE trial dataset at the prespecified timepoints of baseline (time of randomization) and at every follow-up (day 60 and every 6 months until the end of study follow-up). At baseline, we collected data on the following characteristcs: demographics (age, sex, race); presenting symptoms; cardiovascular risk factors (physical activity, obesity, family history of CAD, smoking, hypertension, dyslipidemia, diabetes [treated with diet-only, oral hypoglycemics, insulin]); other cardiovascular disease (cerebrovascular disease, peripheral artery disease, heart failure with New York Heart Association class); and clinical or laboratory variables (blood pressure, heart rate, weight, body-mass index, serum creatinine level, estimated glomerular filtration rate, lipid panel, presence of Q waves on electrocardiogram, predicted atherosclerotic cardiovascular disease (ASCVD) risk scores (Framingham Risk Score\textsuperscript{23} and ASCVD Pooled Cohort Risk Equation\textsuperscript{24}), and predicted pretest probability of CAD using the combined Diamond-Forrester and CASS score.\textsuperscript{2} We collected the following data from the initial CCTA: coronary artery calcium score, number of stenosed vessels, and degree of stenosis within each coronary artery (left main, left anterior descending, left circumflex, and right coronary artery). We collected the following data from each study visit: clinical, laboratory, and electrocardiographic variables, and medications.

Analysis plan

We performed descriptive statistics on baseline demographic data, grouped by coronary status using means with standard deviations for continuous variables, and frequencies and proportions (%) for categorical variables. For comparisons between coronary status groups, we used the one-way analysis of variance test to compare continuous variables and Pearson’s $\chi^2$ test or Fisher’s exact test for categorical variables.

In a post-hoc analysis, we used logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for medication continuation comparing the NOCAD and obstructive CAD groups to the group with normal coronaries, adjusted for potential confounders. All P values $<$ 0.05 were considered statistically significant. All analyses were performed using R version 3.4.3 (R Project for Statistical Computing).

Results

Of the 4996 patients randomized to CCTA in PROMISE, we included 4388 patients who had $\geq 2$ follow-up visits, including a visit at day 60 or month 6. Nearly all patients ($\geq 99.5\%$) underwent CCTA by day 60.

Baseline characteristics

Table 1 describes the baseline characteristics of patients included in our cohort. The mean age was 60.3 years (standard deviation: 8.2); 2997 (52.3\%) were female; 85\% were white; all had symptoms; and 73.2\% presented with chest pain or discomfort as their primary symptom warranting investigation for CAD. Of these, 2132 (48.6\%) had NOCAD, 1707 (38.9\%) had normal coronaries, and 444 (10.1\%) had obstructive CAD. Within the NOCAD group, there was a mean of 2 coronary arteries with nonobstructive disease, and 2023 (94.9\%) patients had “minimal to mild” NOCAD, whereas 109 (5.1\%) had “moderate” NOCAD in at least one coronary artery.

In general, there was a gradient of distribution in risk factors and baseline medication use between patients with normal coronaries and obstructive CAD, with NOCAD patients generally being intermediate (Table 1). For instance, the mean ASCVD Pooled Cohort Risk Equation score was 10.4\% among patients with normal coronaries, 16.5\% in NOCAD patients, and 20.2\% in patients with obstructive CAD ($P < 0.001$). Respective baseline use of combination preventive therapy was 9.2\%, 17.8\%, and 20.4\% among these groups ($P < 0.001$). Compared to patients with obstructive CAD, patients with NOCAD were younger, were more likely to be female and black, were less likely to present with chest pain/pressure as the primary symptom or with typical chest pain, and had lower scores predicting long-term ASCVD risk and pretest probability of CAD. Conversely, patients with NOCAD were older, were more likely to be...
Table 1. Baseline and coronary computed tomography angiography (CCTA) characteristics

| Characteristic                              | Total (n = 4388) | Obstructive CAD (n = 444) | Nonobstructive CAD (n = 2132) | Normal coronaries (n = 1707) | P      |
|---------------------------------------------|------------------|----------------------------|--------------------------------|-------------------------------|--------|
| Demographics                                |                  |                            |                                |                               |        |
| Age, y, mean (SD)                           | 60.3 (8.2)       | 62.6 (8.6)                 | 61.3 (8.2)                     | 58.2 (7.4)                    | < 0.001|
| Female                                      | 2297 (52.3)      | 149 (33.6)                 | 1007 (47.2)                    | 1105 (64.7)                   | < 0.001|
| Race                                        | n = 4349         |                            |                                |                               |        |
| Asian                                       | 116 (2.7)        | 12 (2.7)                   | 54 (2.5)                       | 47 (2.8)                      |        |
| Black                                       | 443 (10.2)       | 23 (5.3)                   | 199 (9.4)                      | 214 (12.6)                    |        |
| Hawaiian                                    | 9 (0.2)          | 2 (0.5)                    | 2 (0.1)                        | 5 (0.3)                       |        |
| Indian                                      | 32 (0.7)         | 3 (0.7)                    | 16 (0.8)                       | 12 (0.7)                      |        |
| Multiracial                                 | 54 (1.2)         | 1 (0.2)                    | 30 (1.4)                       | 20 (1.2)                      |        |
| White                                       | 3695 (85.0)      | 396 (90.6)                 | 1815 (85.8)                    | 1395 (82.4)                   |        |
| Primary symptom                             |                  |                            |                                |                               | 0.002  |
| Chest pain/pressure                         | 3211 (73.2)      | 335 (75.5)                 | 1504 (70.6)                    | 1297 (76.0)                   |        |
| Dyspnea                                     | 634 (14.5)       | 56 (12.6)                  | 350 (16.4)                     | 214 (12.5)                    |        |
| Other                                       | 540 (12.3)       | 53 (11.9)                  | 276 (13.0)                     | 195 (11.4)                    |        |
| Chest pain character                        |                  |                            |                                |                               | 0.005  |
| Typical                                     | 520 (11.9)       | 74 (16.7)                  | 255 (12.0)                     | 175 (10.3)                    |        |
| Atypical                                    | 3403 (77.6)      | 330 (73.4)                 | 1647 (77.3)                    | 1346 (78.9)                   |        |
| Noncardiac                                  | 465 (10.6)       | 40 (9.0)                   | 230 (10.8)                     | 186 (10.9)                    |        |
| Cardiovascular history and risk scores      |                  |                            |                                |                               |        |
| Obesity                                     | 2077/4347 (47.8) | 225 (51.3)                 | 1031 (48.9)                    | 774 (45.6)                    | 0.043  |
| Family history of premature CAD             | 1450/4374 (33.2) | 155 (35.1)                 | 749 (35.2)                     | 514 (30.2)                    | 0.003  |
| Smoking                                     | n = 4387         |                            |                                |                               |        |
| Current                                     | 754 (17.2)       | 101 (22.7)                 | 384 (18.0)                     | 253 (14.8)                    |        |
| Former                                      | 1486 (33.9)      | 161 (36.3)                 | 786 (36.9)                     | 499 (29.2)                    |        |
| Never                                       | 2147 (48.9)      | 182 (41.0)                 | 962 (45.1)                     | 954 (55.9)                    |        |
| Hypertension                                | 2872 (65.5)      | 302 (68.0)                 | 1478 (69.3)                    | 1013 (59.3)                   | < 0.001|
| Dyslipidemia                                | 3021 (68.8)      | 326 (73.4)                 | 1522 (71.4)                    | 1089 (63.8)                   | < 0.001|
| Diabetes                                    | 938 (21.4)       | 120 (27.0)                 | 519 (24.3)                     | 269 (15.8)                    | < 0.001|
| Cerebrovascular disease                     | 2077/4347 (47.8) | 225 (51.3)                 | 1031 (48.9)                    | 774 (45.6)                    | 0.043  |
| Peripheral artery disease                   | 74/4387 (1.7)    | 10 (2.3)                   | 42 (2.0)                       | 18 (1.0)                      | 0.047  |
| Heart failure                               | 160 (3.6)        | 8 (1.8)                    | 80 (3.8)                       | 72 (4.2)                      | 0.057  |
| Framingham Risk Score, mean (SD)            | 21.6 (15.1) n = 4380 | 30.0 (17.8)               | 24.1 (15.2)                    | 15.8 (11.1)                   | < 0.001|
| ASCVD Pooled Cohort Risk Equation, mean (SD) | 14.6 (11.6) n = 4341 | 20.2 (12.9)               | 16.5 (11.7)                    | 10.4 (8.97)                   | < 0.001|
| Combined Diamond-Forrester and CASS, mean (SD) | 53.5 (21.4)        | 61.2 (21.3)               | 55.8 (21.1)                    | 48.1 (20.7)                   | < 0.001|
| Clinical and laboratory parameters          |                  |                            |                                |                               |        |
| SBP, mm Hg, mean (SD)                       | 131 (16.6) n = 4381 | 135 (17.3)               | 132 (16.3)                     | 129 (16.3)                    | < 0.001|
| BMI, kg/m², mean (SD)                       | 30.4 (5.6) n = 4347 | 30.6 (5.5)               | 30.6 (5.7)                     | 30.0 (5.6)                    | 0.009  |
| eGFR, mL/min per 1.73 m², mean (SD)         | 79.3 (18.9) n = 4343 | 76.5 (18.6)               | 79.6 (19.5)                    | 79.7 (18.2)                   | 0.004  |
| LDL-C, mmol/L, mean (SD)                    | 3.00 (0.96) n = 2418 | 2.95 (1.04)               | 2.95 (0.95)                    | 3.08 (0.95)                   | 0.001  |
| Q waves on ECG                              | 197/4349 (4.5)   | 32 (7.3)                   | 102 (4.8)                      | 60 (3.6)                      | 0.003  |
| Medication use at baseline                  |                  |                            |                                |                               |        |
| Combination                                 | 89 (20.4)        | 370 (17.8)                 | 151 (9.16)                     | < 0.001                      |
| Antithrombotic                              | 241 (55.1)       | 1087 (52.4)                | 663 (40.2)                     | < 0.001                      |
| Statin                                      | 246 (56.3)       | 1061 (51.1)                | 636 (38.6)                     | < 0.001                      |
| RAS blocker                                 | 209 (47.8)       | 996 (48.0)                 | 618 (37.5)                     | < 0.001                      |
| β-Blocker                                   | 109 (24.9)       | 551 (26.6)                 | 382 (23.2)                     | 0.062                        |
| CCTA characteristics                         |                  |                            |                                |                               |        |
| Test performed by study day 60              | 442 (99.5)       | 2125 (99.7)                | 1691 (99.1)                    |                               |        |
| No. of vessels with stenoses, median (IQR)  | 1 (1-2)          | 2 (1-3)                    | 0                             |                               |        |
| Calcium score, Agatston units, median (IQR) | 398 (138-824)   | 84 (19-258)                | 0 (0.00-14)                    | < 0.001                      |
| Calcium score, Agatston units, n/N (%)       |                  |                            |                               |                               | < 0.001|

Values are n/N (%), unless otherwise indicated.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CASS, Coronary Artery Surgery Study; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAD, left anterior descending; LCx, left circumflex; LDL-C, low-density lipoprotein cholesterol; RAS, renin-angiotensin system; RCA, right coronary artery; SBP, systolic blood pressure; SD, standard deviation.

* For the obstructive CAD group, this refers only to obstructive lesions and excludes non-obstructive lesions.
Table 2. Patients who continued preventive medications at every follow-up, stratified by coronary status

| Coronary status         | Obstructive CAD (n = 444) | NOCAD (n = 2132) | Normal coronaries (n = 1707) | P     |
|-------------------------|---------------------------|------------------|-------------------------------|-------|
| Follow-up, y, mean (SD) | 2.3 (0.8)                 | 2.3 (0.8)        | 2.3 (0.8)                     | 0.981 |
| Combination therapy     | 55 (12.4)                 | 193 (9.1)        | 56 (3.3)                      | < 0.001|
| Anithrombotic           | 301 (67.8)                | 1003 (47.0)      | 471 (27.6)                    | < 0.001|
| Statin                  | 195 (43.9)                | 719 (33.7)       | 383 (22.4)                    | < 0.001|
| RAS blocker             | 120 (27.0)                | 569 (26.7)       | 366 (21.4)                    | < 0.001|
| β-Blocker               | 112 (25.2)                | 351 (16.5)       | 210 (12.3)                    | < 0.001|

Values are n (%), unless otherwise indicated.

Table 3. Proportion of visits with reported use of preventive medications, stratified by coronary status

| Coronary status         | Obstructive CAD (n = 444) | NOCAD (n = 2132) | Normal coronaries (n = 1707) | P     |
|-------------------------|---------------------------|------------------|-------------------------------|-------|
| Number of visits, mean (SD) | 6.2 (1.7)                 | 6.1 (1.7)        | 6.0 (1.7)                     | 0.024 |
| Proportion of visits with use reported, mean % (SD) | 35 (39)                  | 24 (35)          | 9 (25)                        | < 0.001|
| Anithrombotic           | 88 (24)                   | 69 (38)          | 48 (42)                       | < 0.001|
| Statin                  | 74 (32)                   | 57 (41)          | 37 (43)                       | < 0.001|
| RAS blocker             | 47 (43)                   | 45 (43)          | 34 (43)                       | < 0.001|
| β-Blockers              | 47 (42)                   | 28 (40)          | 21 (36)                       | < 0.001|

CAD, Coronary artery disease; NOCAD, nonobstructive coronary artery disease; RAS, renin-angiotensin system; SD, standard deviation.

Association between coronary status and continuation of preventive medications

Over a mean follow-up of 2.3 years, 193 (9.1%) in the NOCAD group continued combination therapy, vs 55 (12.4%) with obstructive CAD and 56 (3.3%) with normal coronaries (P < 0.001; Table 2). Compared to patients with obstructive CAD, fewer patients with NOCAD continued to use an anithrombotic agent (67.8% vs 47.0%) and a statin (43.9% vs 33.7%), but continuation of RAS blockers was similar (27.0% vs 26.7%). Conversely, NOCAD patients were more likely to continue each individual medication class compared to patients with normal coronaries (Table 2). Continuation of a β-blocker in the NOCAD group (16.5%) was intermediate between the obstructive CAD group (25.2%) and the group with normal coronaries (12.3%).

In post-hoc analysis adjusted for baseline use of combination therapy, age, sex, race, smoking history, dyslipidemia, diabetes, estimated glomerular filtration rate, and coronary artery calcium score, both the NOCAD group (OR 1.74, 95% CI 1.22-2.52, P = 0.00001) and the obstructive CAD group (OR 2.19, 95% CI 1.33-3.61, P < 0.00001) were associated with higher continued use of combination therapy compared to the group with normal coronaries. Combination therapy at baseline was strongly associated with continued combination therapy, independent of coronary status and other confounders (OR 8.72, 95% CI 6.47-11.84). We observed nearly identical patterns with reported use of combination therapy, independent of coronary status and other confounders.

Discussion

In this analysis of the PROMISE trial, we found that use and continuation of combination cardiovascular preventive medications was low regardless of coronary status identified on CCTA. Furthermore, patients with NOCAD identified by CCTA were less likely than patients with obstructive CAD to initiate or continue combination cardiovascular preventive medications, and this was primarily due to lower use of statins and anithrombotic agents. Overall, use of preventive...
medications only modestly increased after identifying NOCAD on CCTA, and it was primarily driven by increased use of antithrombotic agents.

Initial changes to preventive medication following CCTA in our analysis of the PROMISE trial were similar to those observed in the SCOT-HEART trial, as well as other trials evaluating the impact of coronary artery calcium or carotid plaque screening on preventive medication use.16,25-28 For example, there was an approximate 20% increase in use of antiplatelet agents after CCTA in the NOCAD group in both the SCOT-HEART and PROMISE trials, as well as minimal change in the use of RAS blockers.23 The reduced risk of MACE at 5 years in the SCOT-HEART trial has been attributed to this modest increased use of antiplatelet agents and statins in the group with NOCAD identified on CCTA.16,17 However, this finding was not replicated in the

**Table 4. Longitudinal medication use from baseline to month 18**

| Medication     | Baseline | Day 60 | Month 6 | Month 12 | Month 18 | P     |
|----------------|----------|--------|---------|----------|----------|-------|
| **Combination** |          |        |         |          |          |       |
| Obstructive CAD| 89/437 (20.4) | 161/419 (38.4) | 156/429 (36.4) | 160/418 (38.3) | 134/374 (35.8) | < 0.001 |
| NOCAD          | 370/2075 (17.8) | 501/1967 (25.5) | 514/2023 (25.4) | 475/1962 (24.2) | 394/1688 (23.3) | < 0.001 |
| Normal coronaries | 151/1648 (9.2) | 162/1575 (10.3) | 170/1592 (10.7) | 149/1529 (9.7) | 130/1370 (9.5) | 0.618 |
| **Antithrombotic** |          |        |         |          |          |       |
| Obstructive CAD | 241/437 (55.1) | 345/419 (82.3) | 390/429 (90.9) | 374/418 (89.5) | 333/374 (89.0) | < 0.001 |
| NOCAD          | 1087/2075 (52.4) | 1237/1967 (62.9) | 1464/2023 (72.4) | 1405/1962 (71.6) | 1227/1688 (72.7) | < 0.001 |
| Normal coronaries | 663/1648 (40.2) | 673/1575 (42.7) | 784/1592 (49.2) | 766/1529 (50.1) | 670/1370 (48.9) | < 0.001 |
| **Statin**     |          |        |         |          |          |       |
| Obstructive CAD | 246/437 (56.3) | 346/419 (82.6) | 325/429 (75.8) | 308/418 (73.7) | 271/374 (72.5) | < 0.001 |
| NOCAD          | 1061/2075 (51.1) | 1257/1967 (63.9) | 1188/2023 (58.7) | 1118/1962 (57.0) | 955/1688 (56.6) | < 0.001 |
| Normal coronaries | 636/1648 (38.6) | 664/1575 (42.2) | 630/1592 (39.6) | 566/1529 (37.0) | 510/1370 (37.2) | 0.024 |
| **RAS blocker** |          |        |         |          |          |       |
| Obstructive CAD | 209/437 (47.8) | 218/419 (52.0) | 206/429 (48.0) | 206/418 (49.3) | 176/374 (47.1) | 0.643 |
| NOCAD          | 996/2075 (48.0) | 975/1967 (49.6) | 902/2023 (44.6) | 858/1962 (43.7) | 722/1688 (42.8) | < 0.001 |
| Normal coronaries | 618/1648 (37.5) | 585/1575 (37.1) | 571/1592 (35.9) | 506/1529 (33.1) | 480/1370 (35.0) | 0.074 |
| **β-Blocker**  |          |        |         |          |          |       |
| Obstructive CAD | 109/437 (24.9) | 215/419 (51.3) | 206/429 (48.0) | 201/418 (48.1) | 178/374 (47.6) | < 0.001 |
| NOCAD          | 551/2075 (26.6) | 625/1967 (31.8) | 584/2023 (28.9) | 543/1962 (27.7) | 476/1688 (28.2) | 0.005 |
| Normal coronaries | 382/1648 (23.2) | 366/1575 (23.2) | 336/1592 (21.1) | 323/1529 (21.1) | 289/1370 (21.1) | 0.306 |

Values are n/N (%), unless otherwise indicated. CAD, coronary artery disease; NOCAD, nonobstructive coronary artery disease; RAS, renin-angiotensin system.
comparison of MACE between the CCTA and functional testing groups in PROMISE.\textsuperscript{21} Despite changes in preventive medication use among some patients following CCTA, a significant proportion of NOCAD patients remained undertreated after CCTA in both the PROMISE and SCOT-HEART trials. Our analysis of the PROMISE trial exposed an additional treatment gap in low rates of continuation of preventive medications even among patients who were appropriately treated shortly after CCTA. Thus, the benefits gained from increased use of preventive medications among patients diagnosed with NOCAD, as seen in the SCOT-HEART trial, may not be sustained without further interventions to ensure ongoing patient adherence to these medications. Furthermore, continuation of combination therapy was more strongly associated with use of combination therapy prior to CCTA than with coronary status, which suggests that patient factors other than CCTA results mainly influenced combination therapy use. These issues of under-prescribing and low adherence may be further amplified outside of the clinical trial setting. Knowledge translation and quality improvement strategies aimed at raising awareness of NOCAD and improving preventive medication use and continuation among patients with NOCAD may lead to improved outcomes. Clinicians may benefit from the development of focused guidelines for the management of NOCAD, or the addition of NOCAD as part of updates to existing guidelines on secondary prevention in CAD.\textsuperscript{29} The ongoing WARRIOR trial, which is randomizing 4422 women with ischemia and NOCAD or normal coronaries on CCTA to usual care vs combination preventive medications (aspirin plus high-intensity statin plus RAS blocker), will help to guide the management of this at-risk population.

**Limitations**

This study has limitations that warrant discussion. First, this is a post-hoc observational study and is therefore subject to confounding. However, this study is primarily descriptive and is based on a rich dataset from a randomized controlled trial with standardized, prospective data collection. Second, we defined medication continuation based on patient self-reporting at study visits rather than more traditional measures of adherence, such pharmacy fill records or direct pill counts, which were not available in the PROMISE dataset. This definition resulted in a low proportion of continuation among every coronary status group, including patients with obstructive CAD. However, both our primary and secondary outcome definitions provided estimates for medication continuation in patients with obstructive CAD that were consistent with adherence rates using prescription fill records in contemporary cohorts of patients with obstructive CAD or myocardial infarction.\textsuperscript{18,30} Third, reasons for medication changes were not captured in the PROMISE dataset, and it was therefore not possible to identify potentially appropriate reasons not to initiate or continue preventive medications. Finally, we had planned to assess the association between use and continuation of combination preventive medications with MACE; however, it was not possible to provide reliable estimates due to significant selection bias and confounding that could not be adequately mitigated with statistical adjustment.

**Conclusions**

Among patients who underwent CCTA, patients with NOCAD were less likely to use or continue preventive medications compared to patients with obstructive CAD, which was primarily due to lower use of statins and antithrombotic agents. Few patients initiated and adhered to preventive medications after being diagnosed with NOCAD by CCTA. Patients with NOCAD represent an at-risk population with potential for optimization of preventive medications.

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**Disclosures**

The authors have no conflicts of interest to disclose.

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