ORIGINAL RESEARCH

Variations in Use of Optimal Medical Therapy in Patients With Nonobstructive Coronary Artery Disease: A Population-Based Study

Adam Oxner, MD, MSc; Gabby Elbaz-Greener, MD, MHA; Feng Qui, MSc; Shannon Masih, MSc, MPH; Nevena Zivkovic, MSc; Sami Alnasser, MD; Asim N. Cheema, MD; Harindra C. Wijeysundera, MD, PhD

***Background*—**There is a paucity of data on the need for optimal medical therapy (OMT) in nonobstructive coronary artery disease . We sought to understand if there was variation in the use of OMT between hospitals for patients with nonobstructive coronary artery disease, the factors associated with such variation, and its clinical consequences.

***Methods and Results*—**Using a population-level clinical registry in Ontario, Canada, we identified all patients >66 years undergoing coronary angiography for the indication of stable angina, who had nonobstructive coronary artery disease between November 1, 2010, and October 31, 2013. Hierarchical multivariable logistic models were developed to identify the factors associated with OMT use, with median odds ratio used to quantify the degree of variation between hospitals not explained by the modeled risk factors. Clinical outcomes of interest were all-cause mortality and rehospitalization, with follow-up until March 31, 2015. Our cohort consisted of 5413 patients, of whom 2554 (47.2%) were receiving OMT within 1 year. There was a 2-fold variation in OMT across hospitals (30.4%–61.8%). The variation between hospitals was fully explained by preangiography medication use (median odds ratio of 1.21 in the null model and 1.03 in the full model). There was no difference in risk-adjusted mortality (hazard ratio, 0.94; 95% confidence interval, 0.76–1.16); however, patients receiving OMT had a lower risk of all-cause hospital readmission (hazard ratio, 0.89; 95% confidence interval, 0.84–0.95).

***Conclusions*—**There is wide variation in the use of OMT in patients with nonobstructive coronary artery disease, the major driver of which is differences in baseline medication use. **(*J Am Heart Assoc*. 2017;6:e007526. DOI: 10.1161/JAHA.117.007526.)**

Key Words: medical therapy • nonobstructive coronary disease

The mainstay of treatment for stable coronary artery disease (CAD) is optimal medical therapy (OMT) alone or in combination with revascularization, by either coronary artery bypass grafting or percutaneous coronary intervention.[1,2] Multiple landmark studies have established the importance of these recommended therapies; however, this evidence has been principally demonstrated in patients with chronic CAD with significant obstructive coronary lesions.[3] More important, up to 62% of patients with chronic CAD undergoing elective coronary angiography have nonobstructive coronary lesions.[4–6]

Patients with nonobstructive CAD are at increased risk of major adverse cardiovascular events, compared with those with no CAD.[4,7,8] However, there is less guidance on the best treatment for patients with nonobstructive CAD. Indeed, evidence to date, based on the National Cardiovascular Data Registry CathPCI Registry involving >780 US institutions, suggests that medical management in nonobstructive CAD is not as frequently used compared with patients with obstructive CAD.[9] However, there is a paucity of data on practice variation in nonobstructive CAD and its clinical consequences.

Accordingly, the goal of our study was to address these gaps in knowledge. We used a population-level registry of patients with nonobstructive lesions assessed via coronary angiography for the investigation of stable CAD in Ontario, Canada. The specific aims of this study were to characterize the variation in OMT in patients with nonobstructive CAD, identify predictors of variations in management, and determine if such variation was associated with differences in clinical outcomes.

From the Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre (A.O., G.E.-G., H.C.W.), Sunnybrook Research Institute (N.Z., H.C.W.), and Institute for Health Policy Management and Evaluation (H.C.W.), University of Toronto, Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (F.Q., S.M., H.C.W.); and Division of Cardiology, St Michael's Hospital, Toronto, Ontario, Canada (S.A., A.N.C.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/11/e007526/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Harindra C. Wijeysundera, MD, PhD, 2075 Bayview Ave, Ste A202, Toronto, ON M4N 3M5, Canada. E-mail: harindra.wijeysundera@sunnybrook.ca

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Clinical Perspective

What Is New?

- We found that there was low uptake of optimal medical therapy after angiogram confirmed nonobstructive coronary disease and the lack of optimal medical therapy were associated with an increase in hospitalization.

What Are the Clinical Implications?

- Our study suggests that an optimization of medication after angiography is necessary, and the angiography should act as a catalyst for considering this change in the intensity of therapy.

Methods

This study was approved by the Institutional Research Ethics Board at Sunnybrook Health Sciences Centre at the University of Toronto (Toronto, ON, Canada). On the basis of Ontario privacy legislation, the need for informed consent was waived for this analysis, because it was conducted at the Institute for Clinical Evaluative Sciences in Toronto. Consistent with this legislation, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Ontario is the largest province in Canada, with a population of 13.6 million. All residents have universal access to health care and hospital services through a publicly funded healthcare program administered by a single third-party payer, the Ontario Ministry of Health and Long Term-Care. Our study used data collected by the Cardiac Care Network (CCN) of Ontario. The CCN Cardiac Registry captures data from the 19 hospitals that provide invasive cardiac procedures across the province. A prospective clinical registry of all patients undergoing coronary angiography, percutaneous coronary intervention, or coronary artery bypass grafting is maintained by the CCN. The CCN Cardiac Registry contains demographic, comorbidity, procedural, and anatomical variables, which have been validated through selected chart abstractions and core laboratory analyses.[10]

Administrative Databases

Data from the CCN Cardiac Registry were linked using encrypted unique patient identifiers to population-based administrative databases housed at the Institute for Clinical Evaluative Sciences. We used the Canadian Institute for Health Information Discharge Abstract Database and the National Ambulatory Care Reporting Service database, which contain data on all hospitalizations within the province and emergency department visits, respectively. Physician visits and consultations tracked in the fee-for-service claims history were obtained from the Ontario Health Insurance Program physician claims database. Physician demographics, specialization, and workload data were obtained from the Institute for Clinical Evaluative Sciences Physician Database. Data on medication prescriptions were obtained from the Ontario Drug Benefit (ODB) database, which contains drug use information for all patients >65 years, for whom universal drug coverage is provided. Mortality was determined through linkage with vital statistics in the Registered Persons Database.

Patient Selection

All patients undergoing elective coronary angiography between November 1, 2010, and October 31, 2013, for the indication of stable CAD were included. We restricted the cohort to patients who were at least 66 years old with a valid health card at the index angiogram. This would then allow for a 1-year look-back period to ascertain baseline medication use through the ODB database, which is restricted to patients 65 years and older. We excluded patients with revascularization (percutaneous coronary intervention or coronary artery bypass grafting) before their index angiogram and those with a prior myocardial infarction (MI). We excluded both patients with normal coronary arteries and those who had obstructive CAD at their index angiogram. We defined obstructive CAD as >70% obstruction in any of the left anterior descending artery, circumflex artery, or right coronary artery, or >50% obstruction in the left main artery.[11] For patients who had multiple angiograms during the study period, the first angiogram was considered the index angiogram.

Primary Exposure

Our primary exposure of interest was OMT within 1 year after the angiogram, based on prescription data from the ODB database. Because patients could transition into OMT with time, we treated this as a time-varying covariate. We chose a 1-year time period because we anticipate this is to be a period of medical intensification after the index diagnosis of CAD. Consistent with published literature, we defined OMT as the concomitant use of an anti-ischemic medication (β-blocker/calcium channel blocker/nitrate) and a statin in all patients, whereas either an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) was required only in patients with any 1 of left ventricular dysfunction (<50%), diabetes mellitus, hypertension, kidney disease, previous stroke, or peripheral vascular disease.[12] We assumed that once a patient transitioned to OMT, the patient continued to receive OMT for the remainder of the observational period. We estimated the degree of medication compliance by measuring the medication possession ratio,

defined as the proportion of days that a patient was taking the medication from the first prescription date to the end of follow-up.

Although there is no universal definition of OMT, these medications are strongly recommended by contemporary guidelines as class 1 indications and have been used in previous publications investigating the use of OMT in patients with stable CAD.[3,12] Aspirin, although a strong recommendation, was not included in our analysis because it can be obtained over the counter in Ontario, which is not captured in the available databases. As such, we could not reliably quantify aspirin use.

Outcomes

Patients were followed up from the date of their index angiogram to March 31, 2015.

Our primary outcome was all-cause mortality within the follow-up, as defined previously. Our secondary outcomes were all-cause rehospitalization and rehospitalization for nonfatal MI. Nonfatal MI was determined using a validated algorithm of *International Classification of Diseases, Tenth Edition (ICD-10)*, codes.[13,14]

Statistical Analysis

We compared baseline characteristics of patients who were receiving OMT with those who were not receiving OMT. For univariate analyses, *t*-tests were used to compare continuous variables and χ^2 tests were used to compare categorical variables. A hierarchical multivariable logistic regression model was created to determine the adjusted odds ratios (ORs) of patient-, physician-, and hospital-level predictors of receiving OMT within 1 year. Patients were clustered at the hospital level to account for similarities within each institution. The covariates in this model were determined a priori based on known cardiovascular risk factors and typical comorbidities; in addition, we included the baseline use of nitrates/calcium channel blockers/β-blockers/statins/ACE-I/ARB before the angiogram in our models. We assessed for colinearity by variance inflation factors; on the basis of this, we excluded hypertension in the models. As a sensitivity analysis, we repeated these models without including baseline medications, but with all other comorbidities, including cardiovascular risk factors (diabetes mellitus, hyperlipidemia, and hypertension). As an additional sensitivity analysis, we removed all the patients who were receiving OMT at baseline and repeated these models.

To quantify the degree of variation between hospitals in the use of OMT, we calculated the median OR (MOR), which is used for quantifying the magnitude of the effect of clustering when using a multilevel logistic regression model. The MOR is defined as the median of the set of ORs that could be obtained by comparing 2 patients, 1 at higher risk and 1 at lower risk of the outcome, with identical characteristics from 2 different randomly chosen hospitals.[15] Specifically, the MOR is a measure of variation between different hospitals that is not associated with the modeled risk factors.[15] As such, we calculated this metric for the null model (the model with only the random effect) and then sequentially for the models that included only patient factors and then the full model with patient, physician, and hospital factors. We used bootstrapping to obtain 95% confidence intervals (CIs) around the MOR estimates.

Fully adjusted Cox proportional hazards models were developed to examine the relationship between receiving OMT and clinical outcomes. To control for potential immortal time bias, we treated OMT as a time-varying covariate. Robust "sandwich-type" variance estimators were used to account for potential homogeneity in outcomes for clusters of patients treated at the same hospital. As a post hoc analysis, we repeated our models, separately evaluating cardiovascular versus noncardiovascular readmission, based on the *ICD-10* codes found in Table S1.

All data analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC). Statistical significance was considered to be a 2-sided $P<0.05$.

Results

Cohort

A total of 166 299 angiograms were performed from November 1, 2010, to October 31, 2013, of which 68 062 were performed electively to evaluate stable CAD. We identified 5413 patients who met our inclusion criteria (Figure 1). Within 1 year after the index angiography, 2554 (47.2%) of these patients were receiving OMT.

Baseline characteristics of these patients are presented in Table 1. Several differences were noted between the 2 groups. Those patients who were receiving OMT within 1 year had a higher prevalence of cardiac risk factors (ie, hyperlipidemia, hypertension, and diabetes mellitus), as well as comorbid conditions, including prior stroke and peripheral vascular disease. This is reflected by a higher Charlson comorbidity index score in these patients. Interestingly, the non-OMT group had a high prevalence of patients in the higher-income quintiles.

Medication Use

In Table 2, the proportion of patients taking each class of medications is shown, both 1 year before the angiogram (baseline) and in the 1 year after angiography. Within 1 year

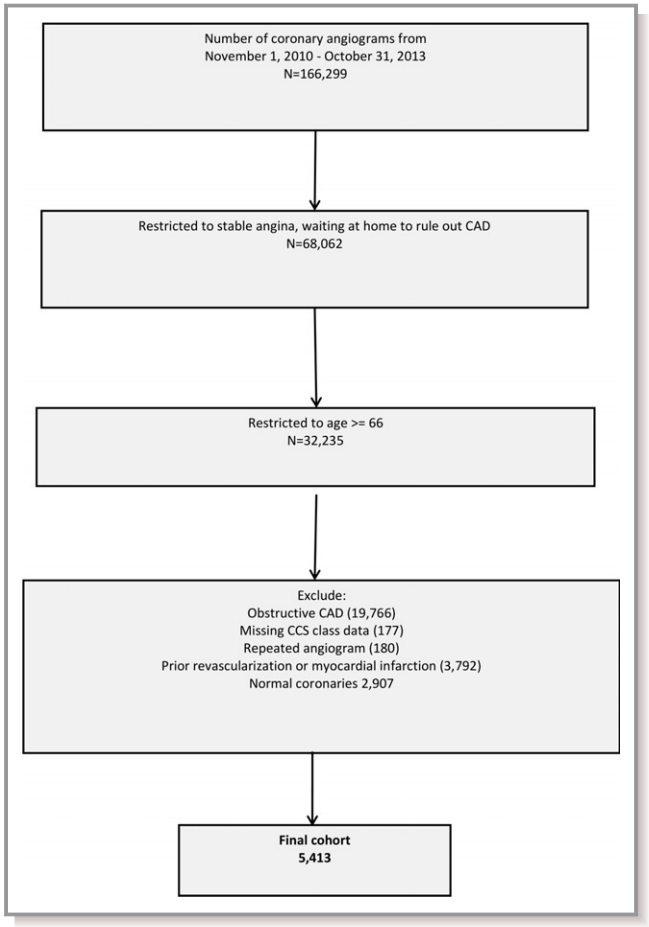

Figure 1. Selection of study cohort. CAD indicates coronary artery disease; and CCS, Canadian Cardiovascular Society.

after angiography, 69.7% of all patients were using ACE-I/ARB, whereas 78.4% were using a statin. Anti-ischemic medication use was lower, at 53.1% for β-blockers, 17.4% for nitrates, and 40.6% for calcium channel blocker. More important, in the OMT group, there were substantially more patients who were already taking each of these classes of medication before the angiogram compared with the non-OMT group; for each medication class other than nitrates, there was an increase in use in the OMT group from baseline to 1 year. In contrast, in the non-OMT group, not only was there substantially lower baseline use, there was also a decrease in the use of all classes of medications, with the exception of statins, from baseline to 1 year. As seen in Figure 2, we observed a 2-fold variation in use of OMT across the sites, ranging from 30.4% to 61.8%.

To determine the degree of medication compliance after OMT, we evaluated the medication possession ratio in the OMT group during the observation period, starting with the first prescription date after angiogram to the end of the follow-up (March 31, 2015) or death date (Table S2). On average, once a patient was categorized in 1 of the OMT medication classes, the patient continued to receive these drugs for >80% of the follow-up. In contrast, only 1.8% to 6.3% of the non-OMT patients transitioned to OMT per 3-month block during the follow-up.

Predictors of Receiving OMT

The most important predictor of receiving OMT in the 1 year after angiography was receiving each of these medication classes at baseline, specifically 1 year before the initial angiogram (Table 3). In particular, receiving an ACE-I/ARB if indicated or a statin before the angiogram was the strongest predictor of receiving OMT in the next year. Reduced left ventricle function (<35%) increased the likelihood of receiving OMT (OR, 1.51; 95% CI, 1.01–2.26) compared with patients with >50% left ventricle function. Patients with high-risk functioning imaging also had a greater likelihood of receiving OMT compared with low-risk patients (OR, 1.21; 95% CI, 1.00–1.47). There were no significant hospital- or physician-related variables that predicted the likelihood of receiving OMT.

Between-Hospital Variation

The MOR for the null model (the model with only the random effect), which quantifies the degree of variation between hospitals not explained by the modeled covariates, was 1.20 (95% CI, 1.18–1.21). To put this value into context, in comparison to the ORs that predict receiving OMT for most patient-level characteristics (Table 3), the MOR was of a lesser magnitude. This suggests that unexplained between-hospital variation was not as relevant as patient-level characteristics for understanding what drives the use of OMT. When patient-level factors were incorporated, almost all the between-hospital variation disappeared, with an MOR of 1.03 (95% CI, 1.03–1.05). To test how much of this variation was associated with baseline medication use, we repeated our model with patient factors but without the inclusion of baseline medications, and found an MOR of 1.22 (95% CI, 1.21–1.23), essentially that of the null model. This suggests that almost all of the variation between hospitals was associated with differences in practice patterns on the use of baseline medication in each of the 5 drug classes of interest.

Sensitivity Analysis: Excluding Baseline OMT

When patients who were receiving OMT at baseline were excluded, we were left with a cohort of 2883 patients. Only 507 (17.5%) of these patients subsequently were given OMT during the 1 year after index angiography. The only predictors of OMT in this cohort were hyperlipidemia (OR, 1.26; 95% CI, 1.02–1.56) and left ventricle function <35% (OR, 1.85; 95% CI,

Table 1. Baseline Characteristics of the Final Cohort by OMT Within 1 Year

Covariates	Total (N=5413)	OMT Within 1 y (n=2554)	No OMT Within 1 y (n=2859)	*P* Value
Patient factors				
Age, y	73.4±5.4	73.6±5.5	73.3±5.4	0.087
Male sex	2661 (49.2)	1247 (48.8)	1414 (49.5)	0.64
Rural residence	692 (12.8)	321 (12.6)	371 (13.0)	0.094
Income quintile*				
1	982 (18.1)	493 (19.3)	489 (17.1)	0.005
2	1115 (20.6)	558 (21.8)	557 (19.5)	
3	1171 (21.6)	560 (21.9)	611 (21.4)	
4	1041 (19.2)	464 (18.2)	577 (20.2)	
5	1079 (19.9)	469 (18.4)	610 (21.3)	
Comorbidities				
Charlson score	0.31±0.90	0.34±0.91	0.28±0.90	0.03
Kidney disease	128 (2.4)	56 (2.2)	72 (2.5)	0.43
Prior stroke	77 (1.4)	49 (1.9)	28 (1.0)	0.004
PVD	258 (4.8)	142 (5.6)	116 (4.1)	0.01
COPD	462 (8.5)	206 (8.1)	256 (9.0)	0.24
Malignancy	138 (2.5)	59 (2.3)	79 (2.8)	0.29
Cardiac risk factors				
Hyperlipidemia	3983 (73.6)	2143 (83.9)	1840 (64.4)	<0.001
Hypertension	4854 (89.7)	2394 (93.7)	2460 (86.0)	<0.001
Diabetes mellitus	2100 (38.8)	1206 (47.2)	894 (31.3)	<0.001
History of smoking	2157 (39.8)	1016 (39.8)	1141 (39.9)	0.92
CCS class				
0	1315 (24.3)	610 (23.9)	705 (24.7)	0.084
1	1010 (18.7)	454 (17.8)	556 (19.4)	
2	2065 (38.1)	985 (38.6)	1080 (37.8)	
3	948 (17.5)	460 (18.0)	488 (17.1)	
4	75 (1.4)	45 (1.8)	30 (1.0)	
LV function, %				
>50	3536 (65.3)	1661 (65.0)	1875 (65.6)	0.12
35–49	400 (7.4)	186 (7.3)	214 (7.5)	
20–34	147 (2.7)	82 (3.2)	65 (2.3)	
<20	40 (0.7)	24 (0.9)	16 (0.6)	
Not done	1290 (23.8)	601 (23.5)	689 (24.1)	
Exercise ECG				
Low risk	1333 (24.6)	592 (23.2)	741 (25.9)	0.017
High risk	1059 (19.6)	479 (18.8)	580 (20.3)	
Uninterpretable	354 (6.5)	172 (6.7)	182 (6.4)	
Not done	2667 (49.3)	1311 (51.3)	1356 (47.4)	

Continued

Table 1. Continued

Covariates	Total (N=5413)	OMT Within 1 y (n=2554)	No OMT Within 1 y (n=2859)	*P* Value
Functional imaging				
Low risk	1766 (32.6)	798 (31.2)	968 (33.9)	0.017
High risk	1453 (26.8)	729 (28.5)	724 (25.3)	
Unknown	2194 (40.5)	1027 (40.2)	1167 (40.8)	
Hospital factors				
Hospital type				0.4
Catheterization only	1308 (24.2)	631 (24.7)	677 (23.7)	
PCI and catheterization only	807 (14.9)	365 (14.3)	442 (15.5)	
CABG, PCI, and catheterization	3298 (60.9)	1558 (61.0)	1740 (60.9)	
Catheterization volume (angiograms/month)	328.4±150.3	329.1±148.5	327.8±151.8	0.749
Physician factors				
PCI physician	2367 (43.7)	1133 (44.4)	1234 (43.2)	0.374
Physician age, y	49.42±9.45	49.49±9.51	49.36±9.39	0.625
Physician sex (male)	5204 (96.1)	2463 (96.4)	2741 (95.9)	0.025
Time since graduation, y	23.9±9.7	24.0±9.8	23.9±9.7	0.85
Total No. of visits (annual)	2939.6±1989.1	2977.1±2100.6	2906.3±1884.2	0.195
Total No. of consultations	975.6±491.2	983.9±516.4	968.2±467.5	0.24

All covariates are expressed as mean±SD or number (percentage). CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; LV, left ventricle; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.
*Income quintile: 1, lowest; 5, highest.

1.10–3.11). However, this model had poor discriminatory power, with a C-statistic of only 0.59.

Clinical Outcomes

Patients were followed up for a mean of 3.7 years after their index angiogram. In the risk-adjusted Cox model, there was no difference in the risk of mortality or readmission for nonfatal MI for those receiving OMT within 1 year of angiography compared with those not receiving OMT (hazard ratio [HR], 0.94; 95% CI, 0.76–1.16, *P*=0.36; and HR, 1.2; 95% CI, 0.83–1.73, *P*=0.33, respectively) (Table 4, Table S3). However, OMT was associated with a lower risk of all-cause hospital readmission after risk adjustment (HR, 0.89; 95% CI, 0.84–0.95; *P*<0.001). In our post hoc analysis, we evaluated cardiovascular versus noncardiovascular readmissions. Most readmissions during the follow-up were for noncardiovascular causes (2078 versus 458 episodes). We found that OMT was associated with a lower risk of noncardiovascular readmissions (HR, 0.88; 95% CI, 0.82–0.93), but not cardiovascular readmissions (HR, 1.03; 95% CI, 0.86–1.22).

Table 2. Patients Receiving Medication at Index Angiography

	All (N=5413)		OMT Group (n=2554)		Non-OMT Group (n=2859)	
Medication	Baseline	1 y	Baseline	1 y	Baseline	1 y
ACE-I/ARB	3654 (67.5)	3775 (69.7)	2274 (89.0)	2468 (96.6)	1380 (48.3)	1307 (45.7)
β-Blocker	2901 (53.6)	2873 (53.1)	1711 (67.0)	1873 (73.3)	1190 (41.6)	1000 (35.0)
Statin	3918 (72.4)	4245 (78.4)	2304 (90.2)	2554 (100.0)	1614 (56.5)	1691 (59.1)
Nitrate	2188 (40.4)	941 (17.4)	1367 (53.5)	643 (25.2)	821 (28.7)	298 (10.4)
CCB	2201 (40.7)	2199 (40.6)	1136 (44.5)	1438 (56.3)	1065 (37.3)	761 (26.6)

Data are given as number (percentage) of patients. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

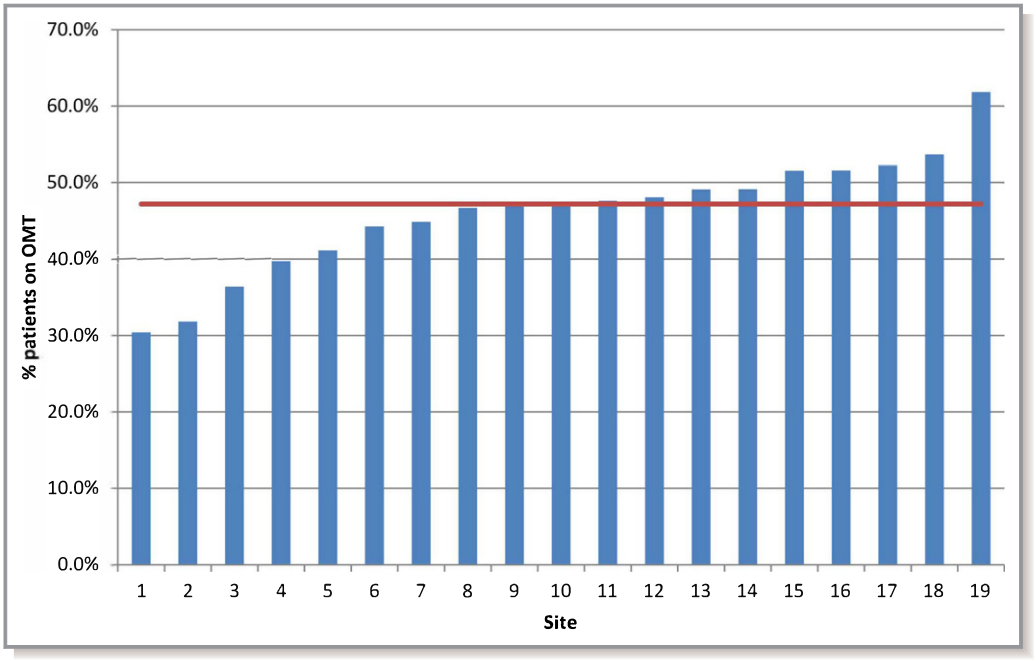

Figure 2. Percentage of patients receiving optimal medical therapy (OMT) by site within 1 year after the coronary angiogram.

Discussion

In this population-based study, we found that ≈47% of patients with nonobstructive CAD were treated with OMT within 1 year; however, there was a 2-fold variation in the proportion of OMT use between institutions. Almost all of this between-hospital variation was associated with differences in baseline medication use. The variation in OMT had clinical consequences because we found that receiving OMT after angiography was associated with a reduction in all-cause hospitalization.

There are clear guidelines for medical management of stable obstructive CAD, which include aspirin, ACE-I, or ARB in appropriate patients, an anti-ischemic agent, and statins.[14] Despite these guidelines for management of stable obstructive CAD, previous work from our group and others has demonstrated that OMT is underused in this patient population.[1,2,14,16] In contrast, there are no definitive guidelines for medical management of nonobstructive CAD, and there is substantial uncertainty as to what constitutes OMT in a population of patients with nonobstructive CAD. We chose a relatively stringent definition, similar to that in obstructive CAD, so as to provide context to our findings.

Our findings add to this body of literature. We demonstrate that fewer than half of patients are prescribed OMT within 1 year of receiving a diagnosis of nonobstructive CAD after angiography. Moreover, there is marked variability between institutions in Ontario. To our knowledge, this is the first study to demonstrate such variation in OMT use. We found several novel insights into the underuse of medications in this population. The strongest predictor of receiving appropriate medications after a confirmatory angiogram was receiving those medications at baseline. In fact, the hospital variation was primarily associated with differences in baseline practice on medication use before the angiogram. Indeed, the angiogram itself does not appear to be a catalyst for medication optimization. This suggests that the increased cardiovascular risk of those with nonobstructive CAD compared with those with no CAD may not be fully appreciated and that there may be room for quality improvement.

The overall low proportion of patients with nonobstructive CAD who were prescribed OMT in our study (47.2%) may be related to several factors. First, patients may have contraindications to the medication classes. Unfortunately, the clinical registry that was used in our study lacks the granularity to determine the degree to which contraindications may have contributed to the lower use rates. Second, there may be a perceived lack of benefit from secondary prevention in the patients without obstructive CAD. This may explain why, in many patients, there was actually a decrease in the use of these medication classes over 1 year after angiography. This is despite the available evidence suggesting that individuals with nonobstructive CAD have an increased risk for adverse clinical outcomes compared with patients with normal coronary arteries.[4,7,8] Moreover, there is evidence that medical therapy (in particular, aspirin and statins) improves clinical outcomes in patients with nonobstructive CAD.[17,18] Consistent with this, we found important differences in

Table 3. Predictors of Receiving OMT Within 1 Year of Catheterization

Covariates	OR (95% CI)	*P* Value
Patient characteristics		
Age (increased risk per y)	1.00 (0.98–1.01)	0.7
Male sex	1.10 (0.94–1.28)	0.22
Rural residence	0.90 (0.72–1.13)	0.35
Income quintile*		
1	Referent	
2	1.08 (0.87–1.35)	0.47
3	0.94 (0.75–1.17)	0.56
4	0.87 (0.69–1.09)	0.22
5	0.97 (0.77–1.21)	0.76
Medical comorbidities		
Charlson score	0.99 (0.89–1.11)	0.88
Kidney disease	0.66 (0.41–1.08)	0.096
Prior stroke	1.47 (0.82–2.65)	0.198
PVD	0.99 (0.72–1.36)	0.95
COPD	0.94 (0.72–1.22)	0.64
Medications		
ACE-I/ARB	8.42 (7.11–9.97)	<0.001
β-Blocker	3.26 (2.83–3.76)	<0.001
Statin	7.19 (5.95–8.68)	<0.001
CCB	2.98 (2.58–3.44)	<0.001
Nitrate	1.07 (0.92–1.24)	0.37
Cardiac risk factors		
Hyperlipidemia	1.03 (0.86–1.23)	0.79
Diabetes mellitus	0.98 (0.84–1.13)	0.75
History of smoking	0.92 (80–1.07)	0.30
CCS class		
0	Referent	
1	0.87 (0.70–1.08)	0.2
2	0.95 (0.79–1.14)	0.58
3 or 4	0.94 (0.75–1.17)	0.57
LV function, %		
>50	Referent	
35–49	1.05 (0.80–1.37)	0.71
<35	1.51 (1.01–2.26)	0.043
Not done	1.05 (0.88–1.25)	0.61
Exercise ECG risk		
Low risk	Referent	
High risk	0.96 (0.77–1.2)	0.74
Uninterpretable	1.06 (0.78–1.45)	0.71
Not done	0.90 (0.75–1.08)	0.26
Functional imaging risk		
Low risk	Referent	
High risk	1.21 (1.00–1.47)	0.046
Not done	1.13 (0.95–1.35)	0.159
Hospital characteristics		
Catheterization volume (monthly)	1.00 (1.00–1.00)	0.4
CABG, PCI, and catheterization	Referent	
Catheterization only	0.99 (0.76–1.30)	0.94
PCI and catheterization only	0.87 (0.66–1.15)	0.31
Physician characteristics		
PCI physician	0.94 (0.79–1.11)	0.45
Age	1.00 (0.99–1.01)	0.61
Total visits billed per y	1.00 (0.96–1.05)	0.83

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LV, left ventricle; OMT, optimal medical therapy; OR, odds ratio; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.
*Income quintile: 1, lowest; 5, highest.

clinical outcomes in patients receiving OMT, particularly being at lower risk for all-cause hospitalization compared with those who were not receiving OMT. Interestingly, in our post hoc analyses, we found that this was primarily attributable to noncardiovascular readmissions. The reasons for this are unclear. It may be because our study was underpowered for cardiovascular causes; alternatively, the use of OMT may be a surrogate for better overall care.

However, we did not find any difference in mortality or readmission for MI. Although our study was not designed to elucidate the reasons for this finding, we can hypothesize that this may be related to the fact that we classified CAD burden dichotomously as either obstructive or nonobstructive, because of limitations in the granularity of the data available in the CCN Cardiac Registry. Patients classified as having nonobstructive CAD may have a range of coronary

Table 4. Relationship Between Receiving OMT and Clinical Outcomes

Outcome	Adjusted HR (95% CI)*	*P* Value
Mortality*	0.94 (0.76–1.16)	0.36
Readmission for nonfatal MI*	1.20 (0.83–1.73)	0.33
All-cause readmission*	0.89 (0.84–0.95)	<0.001

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; and OMT, optimal medical therapy.
*The HR is adjusted for patient, hospital, and physician factors. See Table S4 for the full model.

atherosclerotic burden, from minimal stenosis (ie, <20%) to 69% stenosis. Therefore, if we had separated the nonobstructive CAD group further into groups by degree of stenosis, patterns in the associations between burden of disease, clinical outcomes, and the response to OMT may have emerged. Maddox and colleagues grouped patients into several categories of coronary atherosclerotic burden in a large retrospective cohort study of US veterans and found that the 1-year risks of MI and all-cause mortality were related to severity of CAD.[4]

Our study has important implications for practice and future research. Given the variation across sites was associated with low baseline medication use, this suggests that there was lack of medication optimization after angiography. Our study was not designed to determine the root causes of this, and it is an important area of future study that will likely require a mixed-methods study design. Such research may highlight potential areas for quality improvement.

Our study must be interpreted in the context of several limitations that merit discussion. First, we quantified obstruction based on anatomical angiographic findings without considering functional studies to correlate with other physiologic compromises, such as fractional flow reserve. Second, the provincial drug database (ODB) only includes records of prescriptions that were filled and does not necessarily ensure that there was drug compliance. Moreover, we made the assumption that once patients transitioned to OMT within 1 year, they remained on it. We quantified this by measuring the medication possession ratio and found that, on average, a high proportion of patients remained on the OMT medications. However, this assumption combined with the fact that a small percentage of non-OMT patients transitioned to OMT after 1 year would bias our results to the null. It is reassuring that despite this bias, we found a clinical benefit to OMT, underscoring its importance in patients with nonobstructive CAD. In addition, we were not able to document the use of antiplatelets, specifically aspirin. Finally, we only included patients who were 66 years and older in this cohort to be able to retrieve prescription data from the ODB database (which only includes data for patients 65 years and older) for all included patients up to 1 year before their index angiogram. It is unclear if the results would be any different had we been able to include younger patients in this study, but this should be taken into consideration.

In conclusion, this study found relatively low rates of OMT among patients with nonobstructive CAD. Furthermore, there was up to a 2-fold variation in rates of OMT between institutions, which was strongly associated with differences in preangiography medication use. The use of OMT was associated with improved clinical outcomes. These findings highlight an opportunity for quality improvement.

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Disclosures

None.

References

1. Mancini GB, Gosselin G, Chow B, Kostuk W, Stone J, Yvorchuk KJ, Abramson BL, Cartier R, Huckell V, Tardif JC, Connelly K, Ducas J, Farkouh ME, Gupta M, Juneau M, O'Neill B, Raggi P, Teo K, Verma S, Zimmermann R; Canadian Cardiovascular Society. Canadian cardiovascular society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol*. 2014;30:837–849.
2. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:3097–3137.
3. Chun S, Qiu F, Austin PC, Ko DT, Mamdani M, Wijeysundera DN, Czarnecki A, Bennell MC, Wijeysundera HC. Predictors and outcomes of routine versus optimal medical therapy in stable coronary heart disease. *Am J Cardiol*. 2015;116:671–677.
4. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, Patel MR, Sandhu A, Valle J, Magid DJ, Leon B, Bhatt DL, Fihn SD, Rumsfeld JS. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA*. 2014;312:1754–1763.
5. Patel MR, Dai D, Hernandez AF, Douglas PS, Messenger J, Garratt KN, Maddox TM, Peterson ED, Roe MT. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J*. 2014;167:e842.
6. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.
7. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the women's ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med*. 2009;169:843–850.
8. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H, Prescott E. Stable angina pectoris with no obstructive

coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744.

9. Maddox TM, Ho PM, Roe M, Dai D, Tsai TT, Rumsfeld JS. 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. *Cir Cardiovasc Qual Outcomes*. 2010;3:632–641.
10. Schwalm JD, Wijeysundera HC, Tu JV, Guo H, Kingsbury KJ, Natarajan MK. Influence of coronary anatomy and SYNTAX Score on the variations in revascularization strategies for patients with multivessel disease. *Can J Cardiol*. 2014;30:1155–1161.
11. Bradley SM, Maddox TM, Stanislawski MA, O'Donnell CI, Grunwald GK, Tsai TT, Ho PM, Peterson ED, Rumsfeld JS. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (veterans affairs clinical assessment reporting and tracking). *J Am Coll Cardiol*. 2014;63:417–426.
12. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
13. International Statistical Classification of Diseases and Related Health Problems. Ottawa, Ontario, Canada: CIHI; 2009.
14. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
15. Sanagou M, Wolfe R, Forbes A, Reid CM. Hospital-level associations with 30-day patient mortality after cardiac surgery: a tutorial on the application and interpretation of marginal and multilevel logistic regression. *BMC Med Res Methodol*. 2012;12:28.
16. Wijeysundera HC, Bennell MC, Qiu F, Ko DT, Tu JV, Wijeysundera DN, Austin PC. Comparative-effectiveness of revascularization versus routine medical therapy for stable ischemic heart disease: a population-based study. *J Gen Intern Med*. 2014;29:1031–1039.
17. Hwang IC, Jeon JY, Kim Y, Kim HM, Yoon YE, Lee SP, Kim HK, Sohn DW, Sung J, Kim YJ. Association between aspirin therapy and clinical outcomes in patients with non-obstructive coronary artery disease: a cohort study. *PLoS One*. 2015;10:e0129584.
18. Hwang IC, Jeon JY, Kim Y, Kim HM, Yoon YE, Lee SP, Kim HK, Sohn DW, Sung J, Kim YJ. Statin therapy is associated with lower all-cause mortality in patients with non-obstructive coronary artery disease. *Atherosclerosis*. 2015;239:335–342.

Supplemental Material

Table S1. Cardiovascular disease diagnosis codes

Diagnosis	ICD-9 codes	ICD-10 codes
Cardiovascular (Primary diagnosis code)		
Acute Myocardial Infarction Stroke	410	I21, I22
Heart failure	430, 432, 434, 436,	I60, I61, I63 (excluding I63.6), I64, H34.1
Hypertension	362.3	I50
	428	I10, I11, I12, I13 or I15
	NA	
Unstable Angina	411, 413	I20
STEMI	NA	Subcode R94.30
NSTEMI	NA	Subcode R94.31
Ischemic Stroke	434, 436,	I63, I64, H34.1 (excluding
Hemorrhagic Stroke	362.3	I63.6)
Transient ischemic Attack	430, 431	I60, I61
	435	G45 (excluding G45.4), H34.0
Atrial Fibrillation	427.3	I48
Abdominal Aortic Aneurysm	441.3, 441.4	I71.3, I71.4
Peripheral Arterial Disease	440.2, 443.9, 444.2	I70.2, I73.9, I74.3, I74.4
Non-cardiovascular		
Not meeting criteria for cardiovascular readmission		

ICD- International Classification of Disease

Table S2. Medication possession ratio in the OMT group

drug	Average % of days patient was on the medication from first prescription date (post angiogram) to end of follow-up period (March 31st, 2015) or death date
Beta-Blocker	81.3%
Statins	83.7%
ACE-I/ARB	87.2%
Calcium Channel Blocker	80.4%
Nitrate	36.1%

Table S3. Multivariate cox model of mortality, readmission for non-fetal MI, and all-cause mortality follow up to March 31, 2015

		Death		Myocardial Infarction		All-cause Readmission	
Covariate		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Patient factors							
OMT one year post-cath		0.94 (0.76-1.16)	0.55	1.20 (0.83-1.73)	0.33	0.89 (0.84-0.95)	<0.001
Age		1.07 (1.04-1.09)	<.0001	1.02 (0.98-1.06)	0.28	1.04 (1.03-1.05)	<0.001
Male sex		1.33 (1.03-1.73)	0.03	0.78 (0.56-1.10)	0.159	1.05 (0.98-1.13)	0.195
Rural residence		1.01 (0.65-1.59)	0.95	0.75 (0.34-1.66)	0.47	1.09 (0.98-1.21)	0.116
Income quintile*							
	1	referent		referent		referent	
	2	0.84 (0.67-1.07)	0.163	0.81 (0.44-1.46)	0.48	0.91 (0.82-1.01)	0.065
	3	0.73 (0.56-0.95)	0.021	0.73 (0.34-1.59)	0.43	0.89 (0.80-0.99)	0.04
	4	0.6 (0.43-0.84)	0.003	0.8 (0.39-1.65)	0.55	0.87 (0.78-0.97)	0.014
	5	0.62 (0.44-0.87)	0.006	0.45 (0.19-1.07)	0.072	0.93 (0.85-1.01)	0.1
Comorbidities							
	Charlson score	1.27 (1.13-1.44)	<.0001	1.19 (1.00-1.42)	0.051	1.16 (1.08-1.23)	<0.001
	Kidney disease	1.69 (1.14-2.49)	0.009	1.03 (0.34-3.09)	0.97	1.13 (0.88-1.45)	0.35
	Prior Stroke	0.63 (0.24-1.66)	0.35	1.10 (0.25-4.85)	0.9	0.95 (0.70-1.29)	0.73
	PVD	1.10 (0.71-1.71)	0.66	2.50 (1.32-4.72)	0.005	1.27 (1.12-1.45)	<0.001
	COPD	1.59 (1.09-2.33)	0.017	1.04 (0.47-2.27)	0.92	1.42 (1.18-1.70)	<0.001
	Malignancy	0.74 (0.33-1.69)	0.48	0.71 (0.12-4.17)	0.7	1.06 (0.72-1.56)	0.76
Cardiac risk factors							
	Hyperlipidemia	0.65 (0.51-0.83)	<0.001	1.02 (0.52-1.98)	0.96	0.86 (0.79-0.93)	<0.001
	Diabetes	1.34 (1.06-1.70)	0.015	1.08 (0.77-1.51)	0.65	1.18 (1.08-1.29)	<0.001
	Hypertension	0.94 (0.67-1.33)	0.74	1.20 (0.51-2.85)	0.67	1.08 (0.94-1.24)	0.27
	Smoking history	1.44 (1.04-1.98)	0.028	1.20 (0.65-2.22)	0.57	1.09 (0.98-1.21)	0.126
CCS Class							
	0	referent		referent		referent	
	1	1.07 (0.76-1.50)	0.7	0.39 (0.17-0.91)	0.029	0.86 (0.77-0.96)	0.007
	2	0.73 (0.55-0.97)	0.031	1.06 (0.53-2.13)	0.87	0.82 (0.74-0.9)	<0.001
	3 or 4	0.79 (0.59-1.05)	0.104	0.98 (0.47-2.07)	0.96	0.79 (0.73-0.86)	<0.001
LVEF							

	>50%	referent		referent		referent	
	35-49%	1.32 (0.92-1.89)	0.126	1.48 (0.71-3.09)	0.29	0.99 (0.87-1.12)	0.87
	<35%	1.11 (0.6-2.06)	0.74	2.62 (0.97-7.09)	0.057	1 (0.82-1.22)	0.99
	Not done	0.97 (0.78-1.21)	0.78	1.38 (0.89-2.16)	0.153	0.85 (0.76-0.95)	0.004
Exercise ECG risk							
	Low risk	referent		referent		referent	
	High risk	0.8 (0.49-1.3)	0.37	1.32 (0.50-3.49)	0.58	0.99 (0.82-1.19)	0.89
	Uninterpretable	1.53 (0.85-2.75)	0.153	1.2 (0.48-3.01)	0.7	1.09 (0.88-1.35)	0.43
	Not done	1.49 (0.98-2.26)	0.062	1.87 (0.86-4.1)	0.116	1.39 (1.21-1.6)	<0.001
Functional imaging risk							
	Low risk	referent		referent		referent	
	High risk	1.41 (1.03-1.93)	0.032	0.78 (0.40-1.51)	0.46	1.04 (0.91-1.19)	0.61
	Not done	1.64 (1.16-2.31)	0.005	1 (0.55-1.82)	1	1.13 (1.02-1.26)	0.02
Hospital factors							
Catheterization volume		1.00 (1.00-1.00)	0.67	1.00 (1.00-1.00)	0.125	1.00 (1.00-1.00)	0.96
CABG, PCI and cath		referent		referent		referent	
Cath only		1.14 (0.87-1.49)	0.35	0.84 (0.42-1.67)	0.62	1.07 (0.91-1.26)	0.39
PCI and cath only		1.04 (0.79-1.37)	0.77	1.03 (0.54-1.95)	0.93	1.01 (0.88-1.18)	0.85
Physician factors							
PCI physician		0.93 (0.75-1.17)	0.54	0.79 (0.45-1.39)	0.41	1.03 (0.93-1.14)	0.63
Physician age		0.99 (0.98-1.00)	0.122	1.01 (0.99-1.03)	0.41	1.00 (1.00-1.01)	0.4
Physician visits		1.02 (0.97-1.06)	0.46	0.97 (0.86-1.09)	0.58	1.01 (0.98-1.03)	0.64

ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CABG = coronary artery bypass graft, Cath = catheterization, CCS= Canadian Cardiovascular Society, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ECG = electrocardiogram, HR = Hazard ratio, LVEF = left ventricle ejection fraction, MI = myocardial infarction, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease

*Income quintile: 1=lowest, 5=highest