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ORIGINAL RESEARCH

Lipid-Lowering Medication and Outcomes After Anatomical and Functional Imaging in Suspected Coronary Artery Disease

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ABSTRACT

BACKGROUND Anatomical and functional imaging identify different phenotypes of coronary artery disease (CAD) that may have implications for lipid-lowering medication (LLM).

OBJECTIVES The aim of this study was to assess the associations between LLM and long-term outcomes after combined anatomical and functional imaging in patients with suspected obstructive CAD.

METHODS Consecutive patients (n = 1,973; 41% men; median age: 63 years) underwent coronary computed tomography angiography (CTA) because of suspected CAD. Patients in whom obstructive CAD was not ruled out by CTA underwent ischemia testing by positron emission tomography. Data on LLM purchases were collected until 2 years, and the combined endpoints of death, myocardial infarction, and unstable angina pectoris were assessed at a median of 6.7 years.

RESULTS After imaging, LLM was used by 24% of patients with no CAD, 51% of patients with nonobstructive CAD, 72% of patients with obstructive CAD on CTA without myocardial ischemia, and 91% of patients with myocardial ischemia. The use of LLM decreased during follow-up, with 77% of patients with myocardial ischemia using LLM for 2 years. The use of LLM was associated with a lower annual rate of adverse events in patients with myocardial ischemia (6.1% vs 2.8%; $P = 0.032$) or obstructive CAD without myocardial ischemia (2.9% vs 1.4%; $P = 0.004$) but not in patients with nonobstructive CAD (1.5% vs 1.4%; $P = 0.89$) or no CAD (0.3% vs 0.3%; $P = 0.68$).

CONCLUSIONS The CAD phenotype defined by anatomical and functional imaging guides the use of LLM. The presence of myocardial ischemia and anatomical obstructive coronary lesions were associated with a long-term outcome benefit from LLM. (JACC Cardiovasc Imaging. 2025;18:62-73) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Lipid-lowering medication (LLM) plays a key role in the primary and secondary prevention of coronary artery disease (CAD).[1,2] In patients diagnosed with CAD, LLM is recommended irrespective of cholesterol levels.[1] However, in real-world clinical practice, both undertreatment and incomplete compliance remain as challenges associated with an increased risk for future cardiovascular disease events.[3,4]

Cardiovascular imaging is pivotal in the contemporary diagnostic work-up of chronic CAD because it enables detailed phenotyping of CAD and confers prognostic information to guide treatment decisions.[1] Coronary computed tomography angiography (CTA) enables noninvasive detection of nonobstructive and obstructive coronary atherosclerosis, whereas functional imaging modalities allow detection of myocardial ischemia associated with hemodynamically significant coronary stenosis.[5] In the randomized SCOT-HEART (Scottish COmputed Tomography of the HEART) trial, coronary CTA in addition to standard care, exploiting mainly exercise electrocardiography as a functional test, resulted in a reduced 5-year risk of cardiovascular death or myocardial infarction (MI) compared with standard care alone.[6-8] In this trial, there was increased use of preventive medications in the CTA arm.[7,8] However, real-world data indicate variable use of preventive medications after routine diagnostic testing,[9-16] and there is only limited information on the prognostic impact of LLM in different CAD phenotypes identified by noninvasive diagnostic testing.[16-19]

The aim of this observational study was to evaluate the implementation of LLM and its association with outcomes in patients with different CAD phenotypes identified by combined anatomical and functional imaging (no CAD, nonobstructive CAD, anatomically obstructive CAD without myocardial ischemia, and ischemic CAD) (**Central Illustration**). We assessed LLM purchases in a contemporary real-world cohort of patients who underwent coronary CTA and positron emission tomography (PET) myocardial perfusion imaging because of suspected CAD and evaluated the associations between the use of LLM and the occurrence of death, MI, or unstable angina pectoris (UAP).

METHODS

Patients were selected from a retrospective observational institutional registry including consecutive patients who were referred to coronary CTA for suspected obstructive CAD at Turku University Hospital during 2008-2016. Patients undergoing coronary CTA for primarily other reasons, such as cardiomyopathy or preoperative evaluation, or with previously known CAD were not included. Of 2,210 patients, we excluded patients with nondiagnostic image quality (n = 142) and patients who did not complete the diagnostic protocol (n = 95; ie, did not undergo PET despite anatomical obstructive CAD on CTA). Hence, the final study population consisted of 1,973 patients. An additional 3 patients were excluded from the outcome analysis for incomplete follow-up data. All data in the registry were pseudonymized.

This study complies with the Declaration of Helsinki. The Ethics Committee of the hospital district of southwest Finland approved the study protocol and waived the requirement for written informed consent.

ABBREVIATIONS AND ACRONYMS

CACS = coronary artery calcium score

CAD = coronary artery disease

CTA = computed tomography angiography

LLM = lipid-lowering medication

MI = myocardial infarction

PET = positron emission tomography

SIS = segment involvement score

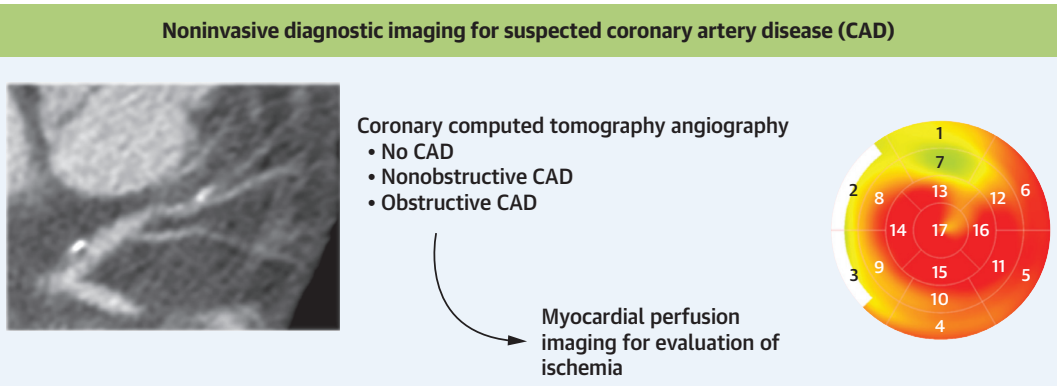
UAP = unstable angina pectoris

IMAGING PROCEDURES AND DEFINITIONS. Coronary CTAs were performed with hybrid scanners containing ≥64-row multidetector computed tomography and PET (GE Discovery VCT or GE D690; General Electric Medical Systems). Before coronary CTA, a nonenhanced coronary artery calcium scan was performed in 1,615 patients (82%). Before the scan, patients were administered intravenous metoprolol (up to 30 mg) to achieve a target heart rate of <60 beats/min and isosorbide dinitrate aerosol (1.25 mg) or sublingual nitrate (800 μg). Prospective electrocardiography-triggered CTA acquisition during diastole was used whenever feasible. Intravenously administered low-osmolal iodine contrast agents (320-400 mg iodine per mL) were used.

According to institutional practice, patients with suspected obstructive CAD (≥50% diameter stenosis) on coronary CTA underwent ischemia testing with ^{15}O-water PET myocardial perfusion imaging during adenosine stress (140 μg/kg/min), usually during the same day, as reported previously.[20] Patients abstained from caffeine for 24 hours before PET. The scans were analyzed by experienced physicians, and the findings were reported to the referring physician in a standardized form.

CAD phenotype was defined based on coronary CTA and PET as no CAD, nonobstructive CAD (<50% diameter stenosis), obstructive CAD without ischemia (≥50% diameter stenosis without myocardial ischemia), and ischemic CAD (≥50% diameter stenosis associated with myocardial ischemia). Myocardial ischemia was defined as abnormal segmental stress myocardial blood flow by ^{15}O-water PET, based on a cutoff (≤2.3 mL/g/min) validated against a fractional flow reserve ≤0.8.[21] Furthermore, the extent of coronary atherosclerosis was classified based on the

CENTRAL ILLUSTRATION **The Interplay of Imaging, Medication, and Outcome in CAD**



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This study focuses on the interplay of noninvasive imaging findings, subsequent use of lipid-lowering medication (LLM), and long-term outcomes in patients with suspected coronary artery disease (CAD). Contemporary imaging modalities were used in accordance with the guideline recommendations in a real-world patient cohort. LLM was assessed based on comprehensive national registry data on drug purchases. Hard adverse events were recorded during a long-term follow-up.

Agatston coronary artery calcium score (CACS) as no calcification (CACS = 0), mild (CACS = 1-99), moderate (CACS = 100-399), or extensive (CACS ≥400). In addition, the segment involvement score (SIS) was calculated as the number of atherosclerotic segments on coronary CTA, and patients with nonobstructive CAD were stratified as having nonextensive (SIS ≤4) or extensive (SIS >4) disease.[16]

LIPID-LOWERING MEDICATION. Data on purchases of LLM were obtained from the national database of the Social Insurance Institution of Finland for a time interval starting 1 year before and ending 2 years after the date of coronary CTA. We only analyzed the purchases of statin and ezetimibe in this study because the number of patients using other types of LLM was negligible (n = <10).

In Finland, LLMs are only available from pharmacies with physician prescription, and all purchases are recorded in the database. Medications are dispensed for a maximum of 3 months of usage. The use of LLM at baseline was defined as any purchase from 6 to 12 months before coronary CTA. The use of LLM after coronary CTA was evaluated for 2 years at 6-month intervals and defined as any purchase during each 6-month period. For outcome analyses, the use of LLM was defined as any purchase within 6 months after coronary CTA and PET.

CLINICAL ENDPOINTS. Clinical patient characteristics were collected from electronic medical records. Diagnosis of dyslipidemia was based on clinical history, current use of LLM, or elevated plasma low-density-lipoprotein cholesterol >3.0 mmol/L or plasma triglycerides >1.7 mmol/L measured within 6 months before coronary CTA.

Information on early (within 6 months after imaging) invasive coronary angiography, percutaneous coronary intervention, and coronary artery bypass graft surgery were collected but were not considered as adverse events. For long-term follow-up, major adverse events including all-cause death, MI, and hospitalization due to UAP were assessed until May 2020. These data were derived from hospital

discharge registry data (Auria Clinical Informatics). Diagnoses of MI and UAP were individually verified from electronic medical records.

STATISTICAL ANALYSES. Continuous variables (showing non-normal distribution by the Shapiro-Wilk test) are presented as median (25th-75th percentile) and compared using an independent-sample Mann-Whitney U test or Kruskal-Wallis test. Categorical variables are presented as count (percentage) and compared using the chi-square test. Bonferroni adjustment was applied to pairwise comparisons. The proportion of patients purchasing LLMs was compared between different time points using McNemar's test, separately for each of the 4 groups based on imaging findings.

Multivariable binary logistic regression analysis including age, sex, cardiovascular risk factors, symptoms, baseline use of LLM, and CAD phenotype as covariates was used to predict purchases of LLM after the diagnostic imaging (within 0-6 months). Based on this logistic regression model, the propensity score was calculated as the individual predicted probability (P) of purchasing LLM after the imaging and was transformed to log odds by $\log[P/(1-P)]$, and log odds was subsequently included as a covariate in Cox regression analysis. The annual (crude) rate of major adverse events is expressed as a percentage for each of the 4 groups based on imaging findings, counted based on the number of adverse events and person-time of follow-up in each group. Univariable and multivariable Cox proportional hazards models were used to assess predictors of long-term outcome. A 2-sided value of $P < 0.05$ was considered statistically significant. The statistical analyses were conducted using IBM SPSS Statistics version 27.

RESULTS

PATIENT CHARACTERISTICS AND CAD PHENOTYPE. A cohort of 1,973 patients with suspected CAD was analyzed (806 men (41%); median age, 63 years [25th-75th percentile, 56-69]). Dyslipidemia was present in 63% of patients, hypertension in 56%, and diabetes in 15%. Patient characteristics are shown in **Table 1**.

As shown in **Figure 1**, 676 patients (34%) had no CAD, 640 (32%) had nonobstructive CAD, 325 (16%) had anatomically obstructive CAD without myocardial ischemia, and 332 (17%) had ischemic CAD. As compared with patients with no CAD, patients with CAD were older, more often men, and more frequently had diabetes, hypertension, dyslipidemia, smoking history, and typical angina (**Table 1**). Among patients with anatomically nonobstructive CAD, 538 (84%) had nonextensive (SIS ≤4) and 102 (16%) had extensive atherosclerosis (SIS >4).

The CACS was 0 in 590 (37%), 1 to 99 in 471 (29%), 100 to 399 in 306 (19%), and ≥400 in 248 (15%) patients. The extent of coronary calcification was on average mild in patients with nonobstructive CAD, moderate in patients with anatomically obstructive CAD, and extensive in patients with ischemic CAD (**Table 1**).

Early revascularizations were performed in 37% of patients with ischemic CAD and 1.2% of patients with obstructive CAD without ischemia. No revascularizations were performed in patients with nonobstructive or no CAD.

USE OF LLM. During the observation period, there were 9,081 purchases of LLM (97.2% statin and 2.8% ezetimibe) (**Table 1**). As shown in **Figure 2**, 27% of patients used LLM at baseline. The proportion of patients using LLM at baseline gradually increased from patients with no CAD to those with ischemic CAD detected on subsequent imaging (overall $P < 0.001$).

An increase in LLM purchases was observed after coronary CTA and PET as compared with baseline in all CAD phenotypes ($P < 0.001$) (**Figure 2**). The proportion of patients purchasing LLM after imaging was related to the CAD phenotype ($P < 0.001$ for overall and pairwise comparisons), ranging from 24% in patients without CAD to 91% in patients with myocardial ischemia. In the presence of nonobstructive CAD or obstructive CAD without ischemia, 51% and 72% of patients purchased LLM, respectively. In nonobstructive CAD, more patients with extensive than nonextensive disease purchased LLM (68% vs 48%; $P < 0.001$) (Supplemental Figure 1). Among patients undergoing early revascularization, 97% purchased LLM. Multivariable logistic regression analysis revealed that in addition to CAD phenotype, age, dyslipidemia, family history of CAD, and previous use of LLM were significant predictors for the purchase of LLM after imaging (**Table 2**).

There was a decrease in purchases of LLM during the 2-year follow-up period ($P < 0.01$ for change) (**Figure 2**). Of patients with myocardial ischemia, 77% continued using LLM at 18 to 24 months after diagnosis. In those with obstructive CAD without ischemia, 58% continued purchasing LLM. At this time, the proportion of patients buying LLM was still associated with the CAD phenotype ($P < 0.001$ for overall and pairwise comparisons). However, only 86% of early revascularized patients used LLM at the end of the 2-year follow-up.

OUTCOMES. During a median follow-up of 6.7 years (25th-75th percentile: 4.8-8.8 years), 130 patients

TABLE 1 Patient Characteristics and Medications at the Time of Imaging, Early Revascularizations, and Outcomes During Long-Term Follow-Up

	No CAD (n = 676)	Anatomically Nonobstructive CAD (n = 640)	Anatomically Obstructive CAD Without Ischemia (n = 325)	Anatomically Obstructive CAD with Ischemia (n = 332)	Total (N = 1,973)	*P* Value
Male	178 (26.3)	265 (41.4)	136 (41.8)	227 (68.4)	806 (40.9)	<0.001
Age, y	58.0 (51.0-65.0)	64.0 (58.0-70.0)	67.0 (61.0-72.0)	65.5 (59.0-70.0)	63.0 (56.0-69.0)	<0.001
Body mass index, kg/m^2	27.0 (24.6-31.6)	28.4 (24.9-32.5)	27.3 (24.8-30.8)	27.8 (24.9-31.2)	27.7 (24.8-31.3)	0.049
Smoking (current or previous)	162 (24.0)	210 (32.8)	114 (35.1)	149 (44.9)	635 (32.2)	<0.001
Diabetes	59 (8.7)	92 (14.4)	63 (19.4)	78 (23.5)	292 (14.8)	<0.001
Hypertension	278 (41.1)	367 (57.3)	227 (69.8)	229 (69.0)	1,101 (55.8)	<0.001
Dyslipidemia	348 (51.5)	424 (66.3)	220 (67.7)	241 (72.6)	1,233 (62.5)	<0.001
Family history of CAD	345 (51.0)	291 (45.5)	143 (44.0)	153 (46.1)	932 (47.2)	0.100
Symptoms						<0.001
Typical AP	110 (16.3)	132 (20.6)	76 (23.4)	99 (29.8)	417 (21.1)	
Atypical AP, noncardiac chest pain, or dyspnea	477 (70.6)	419 (65.5)	210 (64.6)	198 (59.6)	1,304 (66.1)	
Other	89 (13.2)	89 (13.9)	39 (12)	35 (10.5)	252 (12.8)	
Ischemic exercise electrocardiography[a]	216 (46.3)	159 (37.9)	91 (40.4)	114 (48.1)	580 (43.0)	0.023
Coronary artery calcium score[a]	0 (0-0)	41 (7-111)	175 (48-373)	526 (184-1,243)	24 (0-201)	<0.001
Global stress myocardial blood flow, mL/g/min	N/A	N/A	3.7 (3.3-4.4)	2.3 (1.8-2.8)	N/A	<0.001
Medications at the time of imaging[b]						
Statin or ezetimibe	199 (29.4)	282 (44.1)	155 (47.7)	191 (57.5)	827 (41.9)	<0.001
Number of statin and ezetimibe purchases per patient	2.2	4.6	6.2	7.9	4.6	<0.001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	206 (30.5)	291 (45.5)	168 (51.7)	177 (53.3)	842 (42.7)	<0.001
Anticoagulant	44 (6.5)	67 (10.5)	40 (12.3)	33 (9.9)	184 (9.3)	0.012
Antidiabetic or insulin	50 (7.4)	79 (12.3)	55 (16.9)	70 (21.1)	254 (12.9)	<0.001
Beta-blocker	278 (41.1)	306 (47.8)	176 (54.2)	192 (57.8)	952 (48.3)	<0.001
Calcium channel blocker	83 (12.3)	108 (16.9)	80 (24.6)	75 (22.6)	346 (17.5)	<0.001
Organic nitrate	187 (27.7)	232 (36.3)	129 (39.7)	142 (42.8)	690 (35.0)	<0.001
Antiplatelet drug	222 (39.8)	266 (48.4)	143 (49.7)	174 (60.2)	805 (47.8)	<0.001
Early revascularizations[c]						
Early invasive coronary angiography	0 (0.0)	9 (1.4)	18 (5.5)	190 (57.2)	217 (11.0)	<0.001
Early percutaneous coronary intervention	0 (0.0)	0 (0.0)	4 (1.2)	108 (32.5)	112 (5.7)	<0.001
Early coronary artery bypass graft	0 (0.0)	0 (0.0)	0 (0.0)	18 (5.4)	18 (0.9)	<0.001
Early percutaneous coronary intervention or coronary artery bypass graft	0 (0.0)	0 (0.0)	4 (1.2)	123 (37.0)	127 (6.4)	<0.001
Adverse events[d]						
Number of deaths	12 (1.8)	50 (7.8)	23 (7.1)	45 (13.6)	130 (6.6)	<0.001
Number of MIs	2 (0.3)	10 (1.6)	18 (5.5)	16 (4.8)	46 (2.3)	<0.001
Number of UAPs	0 (0.0)	4 (0.6)	2 (0.6)	15 (4.5)	21 (1.1)	<0.001
Composite endpoint (death/MI/UAP)	14 (2.1)	62 (9.7)	41 (12.6)	69 (20.8)	186 (9.4)	<0.001

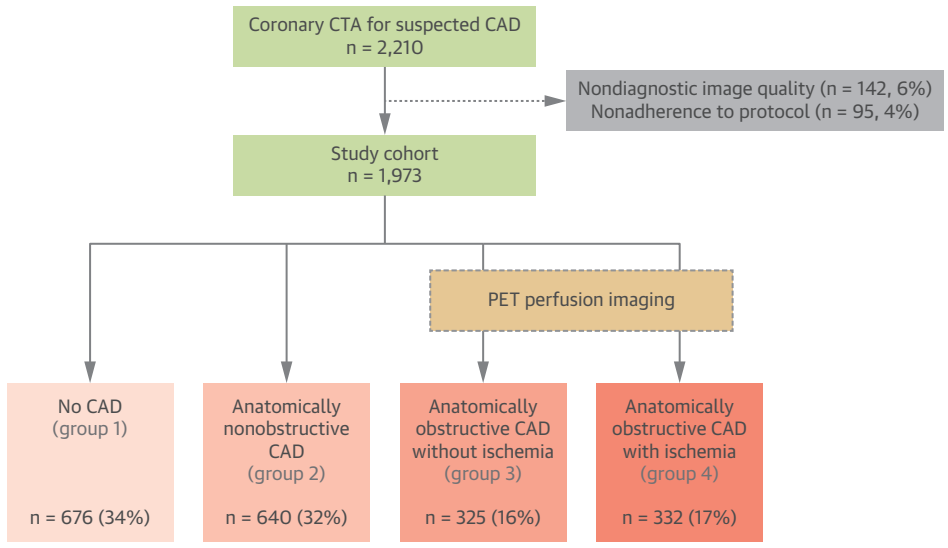
Values are n (%) or median (25th-75th percentile), unless otherwise indicated. [a]Exercise electrocardiography was available for 1,348 patients and coronary artery calcium score available for 1,615 patients. [b]Data for antiplatelet medication were derived from medical records (available for 1,685 patients) and for other medications from comprehensive data from the Social Insurance Institution of Finland (purchases within 6 months before CTA). The total number of statin and ezetimibe purchases per patient was calculated for the 3-year observation period. [c]Early defined as within 6 months after the CTA imaging. [d]Follow-up time for adverse events was a median of 6.7 years (25th-75th percentile, 4.8-8.8 years). Three patients had incomplete follow-up data. Age, body mass index, and coronary artery calcium score were compared using the Kruskal-Wallis test and global stress myocardial blood flow using independent-samples Mann-Whitney U test (non-normal distribution), shown as median (25th-75th percentile). Categorical variables were compared using the chi-square test.

AP = angina pectoris; CAD = coronary artery disease; CTA = computed tomography angiography; MI = myocardial infarction; N/A = not applicable; UAP = unstable angina pectoris.

died, 46 had an MI, and 21 had UAP (Table 1). In 18 patients, UAP led to revascularization. The annual rate of adverse events was 0.3% in patients with no CAD, 1.4% in patients with nonobstructive CAD, 1.8% in patients with obstructive CAD without ischemia, and 3.1% in patients with ischemic CAD ($P < 0.001$).

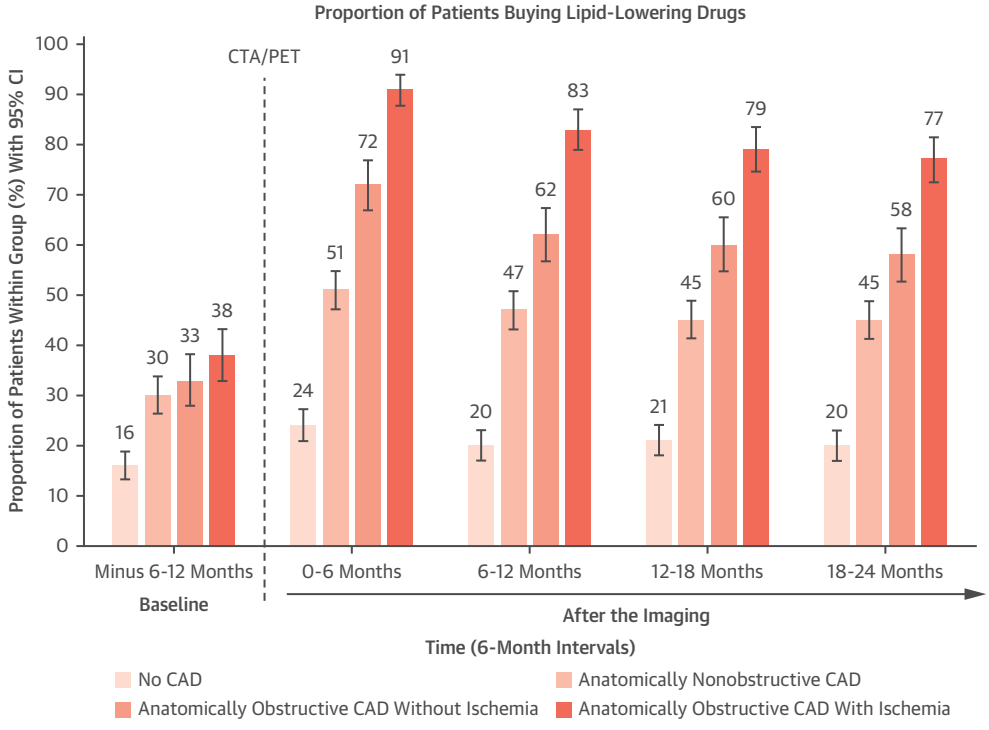
Figure 3 shows the rate of death, MI, and UAP according to CAD phenotype and the use of LLM. Among patients with either ischemic CAD or anatomically obstructive CAD without ischemia, the use of LLM was associated with a lower incidence of death or adverse cardiac events (adjusted $P = 0.032$ and $P = 0.004$, respectively). However, there was no difference in adverse event rate according to the use of LLM among patients with no CAD or nonobstructive CAD. Furthermore, among patients with

FIGURE 1 **Imaging Findings**



Diagnostic work-up of coronary artery disease (CAD) with first-line coronary computed tomography angiography (CTA) and selective downstream positron emission tomography (PET) myocardial perfusion imaging.

FIGURE 2 **Lipid-Lowering Medication**



Proportion of patients purchasing lipid-lowering drugs according to CAD phenotype by CTA/PET imaging. Error bars represent 95% CIs. Abbreviations as in Figure 1.

TABLE 2 Multivariable Binary Logistic Regression Analysis of Predictors for Purchasing Lipid-Lowering Medication Within 6 Months After Diagnostic Imaging (N = 1,973)

	OR (95% CI)	*P* Value
Age (per y)	1.03 (1.01-1.04)	<0.001
Male	1.30 (1.00-1.70)	0.050
Smoking (current or previous)	1.09 (0.84-1.42)	0.508
Diabetes	0.90 (0.62-1.29)	0.562
Hypertension	1.20 (0.94-1.53)	0.134
Dyslipidemia	1.92 (1.49-2.46)	<0.001
Family history of CAD	1.42 (1.12-1.82)	0.005
Symptoms		
Typical AP	Ref.	
Atypical AP, noncardiac chest pain, or exertional dyspnea	0.91 (0.68-1.23)	0.553
Other symptoms	0.71 (0.47-1.08)	0.114
CAD imaging phenotype		
No CAD	Ref.	
Anatomically nonobstructive CAD	2.51 (1.87-3.35)	<0.001
Anatomically obstructive CAD without ischemia	6.88 (4.78-9.90)	<0.001
Anatomically obstructive CAD with ischemia	26.55 (16.58-42.51)	<0.001
Lipid-lowering medication at baseline	11.78 (8.40-16.51)	<0.001

Ref. = Reference; other abbreviations as in Table 1.

extensive nonobstructive CAD (SIS >4), outcome rates were similar among LLM users and nonusers (Supplemental Figure 2).

In multivariable Cox regression analysis, purchasing LLM after coronary CTA and PET was an independent predictor of better long-term outcomes (HR: 0.64 [95% CI: 0.46-0.89]; $P = 0.008$) after adjusting for baseline characteristics and CAD phenotype (Table 3). Consistently, the association between LLM and outcome was similar (HR: 0.63 [95% CI: 0.44-0.91]; $P = 0.014$) when adjusted for propensity score (Table 3). In contrast, previous LLM use (measured at baseline) did not predict long-term outcomes. In contrast to the CAD phenotype defined by coronary CTA and PET imaging, the use of LLM was not significantly associated with the rate of adverse events when patients were stratified according to CACS (Supplemental Figure 3).

DISCUSSION

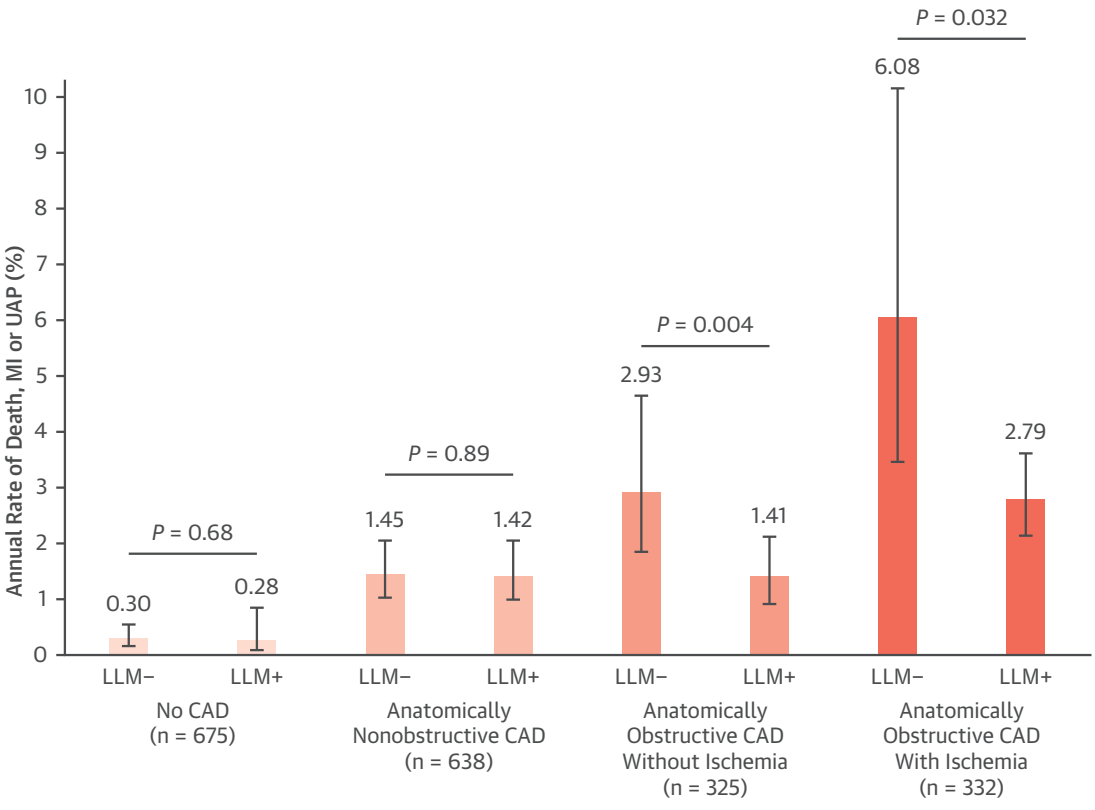
We studied the implementation of LLM and its association with outcome in patients with different CAD phenotypes based on combined anatomical and functional imaging in real-world symptomatic patients with suspected CAD. We found that the presence and severity of CAD were independently associated with the use of LLM within 6 months after coronary CTA and PET perfusion imaging. Although compliance with medication decreased during 2 years, we found that both myocardial ischemia and anatomically obstructive CAD without ischemia were associated with long-term benefit from LLM in terms of lower rates of all-cause death, MI, or UAP.

Hybrid or combined imaging using coronary CTA and functional testing for ischemia enables the accurate detection of nonobstructive and obstructive CAD as well as assessment of the hemodynamic significance of coronary stenosis.[5,22] Although coronary CTA effectively rules out CAD, clinical practice guidelines recommend functional evaluation of CAD before revascularization decisions.[1] Studies have shown that findings of hybrid imaging effectively guide referral to invasive coronary angiography and revascularization.[23-25] However, the use of preventive medications and their impact on outcomes after combined anatomical and functional imaging remain unknown.

We found that LLM was effectively implemented in patients with ischemic CAD (91% used medication after imaging). Previous studies have found variable use of LLM after noninvasive diagnostic tests for CAD.[9-16] In a multicenter registry, findings of diagnostic testing had only a modest effect on medication, with 23% of patients with the most abnormal imaging findings not using LLM.[14] Our results are more in line with other cohorts with LLM prescribed in 90% to 91% of those with obstructive (≥50%) stenosis on coronary CTA.[13,16] Furthermore, our numbers are in line with the coronary CTA arm of the SCOT-HEART trial demonstrating that 86% of patients with CAD were using statins 1 year after the imaging.[8] In line with our previous study, patients with ischemic CAD had the highest rate of death, MI, or UAP (annual rate, 3.1%).[20] Our current study extends previous findings in that LLM was associated with a 54% reduction in the annual rate of adverse events among ischemic patients.

The use of LLM was variable in patients with nonobstructive CAD (51%) and obstructive CAD without myocardial ischemia (72%). These numbers are consistent with previous studies evaluating statin prescriptions in patients with nonobstructive CAD but lower than in patients with obstructive CAD.[16-19] We do not have detailed information on the reasons for underuse of LLM, but it has been hypothesized that communication of test results and their clinical significance is an important factor.[14] Our results are consistent with previous studies[16-19] pointing to the need to inform both patients and physicians about the benefits of LLM in patients with coronary atherosclerosis even in the absence of ischemic CAD, particularly in the presence of anatomically

FIGURE 3 **Long-Term Outcomes**



Annual (crude) long-term incidence of death, myocardial infarction (MI), or unstable angina pectoris (UAP) in patients purchasing lipid-lowering medication (LLM+) vs not purchasing (LLM−) during the 6-month period after diagnostic imaging, categorized by CAD phenotype. *P* values were adjusted for univariable predictors of events, including age, sex, diabetes, hypertension, and symptoms. Error bars represent 95% CIs. Abbreviations as in Figure 1.

obstructive CAD. Patients with coronary atherosclerosis but no flow-limiting coronary stenosis are frequently encountered in the coronary CTA-based diagnostic work-up of chest pain patients, constituting 49% of the current study cohort. Although annual rates of death, MI, and UAP were lower (1.4% and 1.8% in patients with nonobstructive CAD and obstructive CAD without ischemia, respectively) than those with myocardial ischemia, a numerically large proportion (54%) of adverse events occurred in this population, highlighting the need for preventive therapies.

In large registries, statin use was associated with reduced all-cause mortality in patients with nonobstructive coronary atherosclerosis (<50% stenosis) but not in the absence of coronary atherosclerosis.[17,18] The study by Hulten et al[16] suggested that statin use after coronary CTA is associated with a reduced risk of cardiovascular death or MI in patients who show extensive nonobstructive CAD, defined as atherosclerotic plaque in >4 segments. Øvrehus et al[19] found that the prognostic benefit of statin use in patients with nonobstructive coronary atherosclerosis on coronary CTA was proportional to the extent of coronary calcification. Our study extends these by comparing the effect of LLM on outcomes in patients with obstructive CAD without ischemia vs pure nonobstructive CAD. We found that in obstructive CAD without ischemia, the use of LLM was associated with a 52% reduction in the annual rate of death, MI, or UAP, which is similar to patients with myocardial ischemia. This finding is consistent with studies showing that LLM, statins in particular, slow the progression of coronary atherosclerosis and also modify atherosclerotic plaque composition, resulting in its stabilization.[26]

We found similar outcomes in patients who used LLM vs those who did not use LLM in the presence of pure nonobstructive CAD or normal coronary arteries. A possible explanation is a low burden of coronary

TABLE 3 Cox Proportional Hazards Regression Analysis Showing Predictors of Long-Term Outcome (Composite Endpoint of All-Cause Death, MI, or UAP) (N = 1,973)

	Univariable		Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*P* Value	Model 1 HR (95% CI)[a]	*P* Value	Model 2 HR (95% CI)[b]	*P* Value	Model 3 HR (95% CI)[c]	*P* Value
Age, per y	1.07 (1.06-1.09)	<0.001	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001		
Male	1.45 (1.09-1.94)	0.011	1.35 (0.99-1.85)	0.059	1.37 (1.00-1.87)	0.048		
Smoking (current or previous)	1.27 (0.95-1.71)	0.110						
Diabetes	1.69 (1.19-2.40)	0.003	1.27 (0.88-1.83)	0.210	1.29 (0.90-1.85)	0.165		
Hypertension	1.87 (1.37-2.55)	<0.001	1.27 (0.92-1.76)	0.147	1.30 (0.94-1.80)	0.107		
Dyslipidemia	1.00 (0.75-1.35)	0.977						
Family history of CAD	0.75 (0.56-1.01)	0.054						
Symptoms								
Typical AP	Ref.		Ref.		Ref.			
Atypical AP, noncardiac chest pain, or exertional dyspnea	0.73 (0.52-1.02)	0.063	0.85 (0.61-1.20)	0.352	0.84 (0.60-1.18)	0.311		
Other symptom	0.55 (0.32-0.95)	0.033	0.68 (0.39-1.18)	0.171	0.66 (0.38-1.14)	0.135		
CAD imaging phenotype								
No CAD	Ref.		Ref.		Ref.			
Anatomically nonobstructive CAD	4.86 (2.72-8.69)	<0.001	3.21 (1.77-5.81)	<0.001	3.53 (1.94-6.41)	<0.001		
Anatomically obstructive CAD without ischemia	6.16 (3.36-11.30)	<0.001	3.31 (1.76-6.23)	<0.001	4.00 (2.09-7.62)	<0.001		
Anatomically obstructive CAD with ischemia	10.26 (5.77-18.22)	<0.001	5.77 (3.13-10.64)	<0.001	7.51 (3.95-14.28)	<0.001		
Lipid-lowering medication at baseline	1.48 (1.09-2.00)	0.011	0.94 (0.68-1.29)	0.699				
Lipid-lowering medication after imaging, 0-6 mo	1.51 (1.12-2.03)	0.006			0.64 (0.46-0.89)	0.008	0.63 (0.44-0.91)	0.014
Propensity score (log odds)	1.31 (1.22-1.40)	<0.001					1.39 (1.28-1.51)	<0.001

[a]Multivariable model 1 includes age, male, diabetes, hypertension, symptoms, imaging findings, and lipid-lowering medication *at baseline*. [b]Multivariable model 2 includes age, male, diabetes, hypertension, symptoms, imaging findings, and lipid-lowering medication *after imaging* (0-6 mo). [c]Multivariable model 3 includes propensity score and lipid-lowering medication *after imaging* (0-6 mo).
Abbreviations as in Tables 1 and 2.

atherosclerosis, based on the extent of coronary calcification (an average CACS of 41 in patients with nonobstructive CAD vs 175 in patients with obstructive CAD without ischemia), as well as the number of atherosclerotic segments (SIS ≤4 in 84% of patients with nonobstructive CAD). Previous studies have found the highest survival difference between LLM users and nonusers in individuals with a CACS >100 and SIS >4.[16,19,27] When we classified patients according to CACS alone or stratified nonobstructive patients according to SIS, outcomes were not statistically different between patients using vs not using LLM, suggesting the presence of obstructive lesions on coronary CTA or myocardial ischemia on PET provides incremental information on the prognostic benefit from LLM. However, the statistical power of our study is limited by the low number of events in patients with nonobstructive CAD, the relatively low number of patients showing extensive (SIS >4) nonobstructive CAD, and CACS not being measured in all patients.

Of the patients with normal coronary anatomy, around 20% continued using LLM, which is a relatively low number in relation to the reported 52% prevalence of dyslipidemia in this group. Although the outcome of such patients was excellent, with a 0.3% annual rate for the composite endpoint, our study does not rule out potential benefits of LLM beyond the median follow-up of 6.7 years.[28] Furthermore, it was demonstrated in the PESA study cohort that the impact of low-density-lipoprotein cholesterol and systolic blood pressure on the progression of subclinical atherosclerosis (determined by carotid and femoral vascular ultrasound) was particularly pronounced in young subjects.[29] These studies as well as many other prevention studies point to the importance of adequate long-term control of cardiovascular risk factors based on total risk factor burden even in the absence of obstructive atherosclerotic disease.

Our results are in line with previous studies showing that lipid-lowering therapy is underused in CAD and a large fraction of patients do not comply with therapy.[3,4,30] In our study, the use of LLM decreased irrespective of imaging findings, even in patients who underwent revascularization, toward the end of the 2-year follow-up, thereby extending the existing literature on compliance with LLM in patients undergoing coronary CTA for suspected CAD. Also consistent with our study results, a study in asymptomatic individuals participating in a health-screening program showed that the use of statins increased from 6% at baseline to 34% at 90 days after detection of atherosclerosis by coronary CTA but then decreased to 20% at the 18-month follow-up.[12] We do

not have data on reasons underlying the underuse of LLM, but side effects have been identified as a major reason for discontinuing statins, although the evidence suggests that benefits of statins clearly outweigh any safety concerns in secondary prevention.[31,32] Other patient-related factors, such as financial or social circumstances and poor health literacy, may also play a role.[1] In a randomized study, coronary CTA-based education intervention effectively improved cholesterol levels.[33] Our study highlights the need for action to improve compliance with preventive therapies after diagnostic testing.

STUDY LIMITATIONS. Our findings extend knowledge as we report real-world use and compliance with LLM in different CAD phenotypes based on noninvasive anatomical and functional diagnostic testing and found the use of LLM after diagnostic testing to be associated with a reduced risk of adverse events among patients with anatomical obstructive CAD with or without myocardial ischemia. Given the challenges in measuring medication compliance, a strength of our study is the use of comprehensive national registry data on purchases of LLM, reflecting the actual use of medication better than prescriptions or patient-reported use alone, which have been used in most previous studies. Recording drug purchases within 6-month time intervals probably allowed the capturing of all purchases because the drug dose is dispensed in Finland for an individual patient for a maximum of 3 months. In addition, it is unlikely that a patient would continue buying medication regularly if not using it. However, a limitation of the analysis is that the data on drug dosage and change in drug dose were not available.

Because all scans were performed as part of a clinical routine and interpreted by a number of trained physicians, we do not have detailed data on interobserver or intraobserver variability. Because only patients with suspected obstructive CAD based on CTA underwent PET, we do not have information on the prevalence of coronary microvascular dysfunction. However, we have found a relatively low prevalence of microvascular dysfunction in a comparable (but distinct) low-risk cohort.[34] At our center, imaging findings are communicated to the referring physician responsible for the management decisions. Because there are no specific institutional guidelines, our results are representative of lipid-lowering management decisions by individual physicians. However, we do not have access to detailed information on physician- and patient-related reasons for not using LLM.

The study cohort underwent imaging in 2008-2016, allowing the assessment of long-term outcomes, and new LLMs were not available at the time. Furthermore, the purchases of aspirin could not be analyzed because of a lack of comprehensive national registry data. Adverse events were based on hospital discharge registry data, and therefore nonfatal events not leading to hospital admittance could not be evaluated. Moreover, we do not have comprehensive follow-up data on blood cholesterol levels, but previous studies have reported that target levels of low-density-lipoprotein cholesterol are often not achieved.[4,33]

Importantly, we cannot rule out residual confounding related to the retrospective study design despite using multivariable regression models and propensity score adjustment. For example, subjects complying with medication may be healthier on average (healthy user bias). Finally, because of the small number of events in patients with no CAD or nonobstructive coronary atherosclerosis, average follow-up limited to 6.7 years, and lack of follow-up data on biomarkers, our study does not exclude beneficial effects of LLM in this subgroup.

CONCLUSIONS

Advanced noninvasive diagnostic testing with the use of combined anatomical and functional imaging guides the use of LLM in patients with suspected CAD. Compliance with LLM declined during the 2 years of follow-up and warrants special attention. Obstructive CAD and myocardial ischemia are associated with prognostic benefit from LLM.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Noninvasive imaging findings highly impact the subsequent use of LLM in real-world clinical practice of suspected CAD. The presence of obstructive CAD or myocardial ischemia on noninvasive imaging are associated with a long-term prognostic benefit from LLM.

TRANSLATIONAL OUTLOOK: The declining compliance with LLM over time, even in patients with ischemic CAD and/or myocardial revascularization, warrants special attention in clinical patient care. More detailed plaque characterization might enable even better identification of patients who will benefit from LLM, especially in nonobstructive CAD.

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APPENDIX For supplemental figures, please see the online version of this paper.