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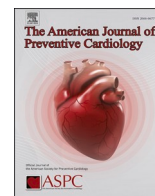
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Trends in LDL-C following coronary angiography involving assessment by fractional flow reserve in obstructive vs non-obstructive coronary artery disease

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ABSTRACT

Background: We sought to determine whether management of LDL-C following invasive angiography and assessment by fractional flow reserve (FFR) differs between those with obstructive vs non-obstructive CAD.

Methods: Retrospective study of 721 patients undergoing coronary angiography involving assessment by FFR between 2013 and 2020 at a single academic center. Groups with obstructive vs non-obstructive CAD by index angiographic and FFR findings were compared over 1 year of follow-up.

Results: Based on index angiographic and FFR findings, 421 (58%) patients had obstructive CAD vs 300 (42%) with non-obstructive CAD, mean (\pm SD) age 66 ± 11 years, 217 (30%) women, and 594 (82%) white. There was no difference in baseline LDL-C. At 3-months follow-up, LDL-C was lower than baseline in both groups, with no between group difference. In contrast, at 6-months, median (Q1, Q3) LDL-C was significantly higher in non-obstructive vs obstructive CAD (LDL-C 73 (60, 93) vs 63 (48, 77) mg/dL, respectively ($p = 0.003$), ($p = 0.001$ in multivariable linear regression)). At 12-months, LDL-C remained higher in non-obstructive vs obstructive CAD (LDL-C 73 (49, 86) vs 64 (48, 79) mg/dL, respectively, although not statistically significant ($p = 0.104$)). The rate of high-intensity statin use was lower among those with non-obstructive CAD vs obstructive CAD at all time points ($p < 0.05$).

Conclusions: After coronary angiography involving FFR, there is intensification of LDL-C lowering at 3-months follow-up in both obstructive and non-obstructive CAD. However, by 6-months follow-up LDL-C is significantly higher among those with non-obstructive CAD vs obstructive CAD. Following coronary angiography involving FFR, patients with non-obstructive CAD may benefit from greater attention to LDL-C lowering to reduce residual ASCVD risk.

1. Introduction

The introduction of hemodynamic assessment of coronary artery disease by fractional flow reserve (FFR) has been a pivotal advance in the ability to risk stratify patients and weigh the risks and benefits of an interventional vs medical treatment approach. While these tools for hemodynamic assessment of coronary artery lesions aid in decision-making around revascularization, it is unknown whether performing FFR as a part of distinguishing obstructive from non-obstructive CAD impacts treatment decisions with regard to medical therapies, including

lipid-lowering therapies [1]. An area of particular uncertainty is the management of patients who have moderate coronary artery disease (thus prompting a hemodynamic assessment of one or more coronary lesions), but who are found to have non-obstructive CAD by FFR. Studies support the conclusion that significant “residual risk” for major adverse cardiovascular events (MACE) exists among those with non-obstructive CAD treated with medical therapy [2–5]. There is also significant room for improvement in the guideline-directed use of lipid-lowering therapy to reduce ASCVD risk among both those with obstructive and non-obstructive CAD, including both statins and non-statin

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lipid-lowering therapies with proven benefit [6–16]. These treatment patterns likely relate at least in part to patient underestimation of their risk for ASCVD and patient uncertainty of the reasons for taking lipid lowering therapy and the end treatment goals. Treatment is also influenced by side-effects from lipid-lowering therapies (especially statins), and uncertainty among clinicians surrounding recommended intensity of medical therapy for those with non-obstructive CAD [17,18]. In this study, we sought to examine practice patterns in obstructive vs non-obstructive CAD defined by FFR and visual angiographic assessment by comparing groups over 1 year with regard to: 1) changes in LDL-C 2) statin and non-statin lipid-lowering therapy, and 3) rate of 1-year MACE.

2. Methods

2.1. Study design and population

We performed a retrospective chart review involving all patients who underwent hemodynamic assessment using FFR at the University of California San Diego (UCSD) between 2013 and 2020. Patients underwent hemodynamic assessment for either ACS or non-ACS indications.

Patients were categorized as having obstructive CAD based on having an index FFR ≤ 0.8 or by visual assessment. Patients without hemodynamically or visually significant CAD were categorized as having non-obstructive CAD. If more than one vessel was assessed via FFR, then obstructive vs. non-obstructive categorization was based on the most severe lesion observed during the assessment. If a patient had more than one FFR assessment, baseline (index) was defined as the earliest documented exam.

Baseline characteristics were collected at the time of index FFR assessment, including patient demographics, comorbid ASCVD diagnoses/risk factors, prior diagnostic testing, FFR and revascularization data, medications, and relevant laboratory values. Follow-up data on medication utilization and laboratory values were collected at 3, 6, and 12-month follow-up time points (only one follow-up time point in a 12-month timeframe was required for study eligibility). A medication was documented as new at each follow-up time point if it was not listed as an active medication at any previous time point. When listed in the medical record at a given time-point, medications were considered as being an active part of a patient's treatment regimen. The occurrence of MACE) at any point between baseline and one year of follow-up was documented. MACE was defined by the occurrence of myocardial infarction (MI), cardiovascular death, cerebrovascular accident (CVA), hospitalization for unstable angina (UA), or coronary revascularization via percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.

Patients were excluded from the study if FFR was being performed for post-heart transplant assessment, assessment being conducted on a non-coronary vessel (e.g. pulmonary or renal arteries), or if there was no follow-up data at any time point up to 12 months. This study was approved by the Institutional Review Board of UCSD and informed consent was not required given the retrospective nature of this study.

2.2. Statistical analysis

Data are presented as relative frequency (proportions) for categorical variables, and as mean \pm SD or median (Q1, Q3) for continuous variables. Significance tests between groups were performed using Mann-Whitney U test or independent sample *t*-test for continuous variables, and chi-square test for categorical variables. The analyses were performed at baseline, 3, 6, and 12-months. A multivariable linear regression was fitted to determine if there is a difference in LDL-C between obstructive and non-obstructive CAD groups at 3, 6, and 12-months, adjusted for demographic and clinical factors considered as potential confounders. Outcomes were log transformed for fitting the regression model. A multivariable logistic regression model was fitted to assess the association between obstructive vs non-obstructive CAD at index exam

and MACE at 12-months, adjusted for demographic and clinical factors considered as potential confounders. For all statistical analyses, $p < 0.05$ was considered statistically significant using two-sided tests. Analyses were performed in SPSS v28 (IBM, Armonk, New York) and R 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Demographics and baseline characteristics

We identified 721 patients having undergone coronary angiography involving FFR assessment at UCSD between 2013 and 2020. Among these, 421 (58%) had obstructive CAD vs 300 (42%) with non-obstructive CAD, as defined by the findings of their index FFR and angiogram. In the obstructive CAD group, 225 (53%) were defined as having obstructive CAD by FFR ≤ 0.8 , while 196 (47%) had FFR > 0.8 , but angiographic evidence of obstructive CAD (i.e. FFR was performed in 1 or more vessel(s) and disease in the areas assessed by FFR proved to be non-obstructive (>0.8), but 1 or more vessel(s) showed angiographic evidence of obstructive CAD). Most FFR assessments were performed for a non-ACS indication (557 (77%)), however, more were performed in the context of ACS among those with obstructive vs non-obstructive CAD (123 (29%) vs 41 (14%), respectively, $p < 0.001$). In the obstructive CAD group, 363/421 (86%) underwent PCI at the time of the index FFR assessment. This includes 14 patients in whom PCI was performed at a follow-up time-point after the index exam, but based on the index angiogram results. None of the patients with non-obstructive CAD underwent PCI at the time of their index angiogram. Additional details on angiographic and FFR findings are included in supplemental materials (Table S1). Mean (\pm SD) age was 66 ± 11 yrs, with 217 (30%) women, and 594 (82%) white. Compared to the obstructive CAD group, there were more women in the non-obstructive CAD group ($p = 0.004$). History of any ASCVD (ACS (UA/MI), PCI, CABG, PAD, TIA/CVA) prior to the index angiogram and FFR assessment was greater among those with obstructive (270 (64%)) vs non-obstructive CAD (149 (50%)) ($p < 0.001$). Diabetes (281 with type 2 diabetes mellitus (T2DM), 7 with type 1 diabetes mellitus) was also more prevalent among those with obstructive CAD (186 (44%) vs non-obstructive CAD (102 (34%)), $p = 0.006$). There was also a greater number of current smokers among those with obstructive CAD (47 (11%) vs non-obstructive CAD (17 (6%)), $p = 0.011$) (Table 1).

3.2. LDL-C and lipid-lowering therapy after index coronary angiogram involving FFR

Baseline median (Q1, Q3) LDL-C was similar in both groups: 79 (54, 106) mg/dL (obstructive CAD) and 76 (55, 102) mg/dL (non-obstructive CAD) ($p = 0.494$). Across all time-points, there were more patients with an LDL-C measurement in the obstructive vs non-obstructive CAD groups (661 vs 402, respectively, $p = 0.002$ (sum of patients with an LDL-C measurement across baseline, 3 mo., 6 mo., and 12 mo.). At 3 months, median LDL-C was lower compared to baseline in both those with obstructive and non-obstructive CAD, with no between group difference ($p = 0.926$) (Fig. 1, Table 2). Comparing all lipid-lowering therapies, there was a similar number of new statins initiated in each group at 3 months ($p = 0.626$), but greater total statin use in the group with obstructive CAD ($p = 0.018$) (Table 3). There was no difference in the number of patients at 3 months with LDL-C < 55 or 70 mg/dL (Table 4).

However, at 6 months, LDL-C was significantly lower in obstructive vs non-obstructive CAD (LDL-C 63 (48, 77) vs 73 (60, 93) mg/dL, respectively ($p = 0.003$) (Fig. 1, Table 2). At 6 months, obstructive CAD predicted lower LDL-C in a model adjusted for age, sex, BMI, race, ethnicity, and history of dyslipidemia among other variables ($p = 0.001$) (Table S2). Compared to non-obstructive CAD, there was greater total statin use ($p = 0.045$) by 6 months in those with obstructive CAD

Table 1

Baseline demographics of 721 patients undergoing hemodynamic assessment by FFR, comparing those with findings of obstructive vs non-obstructive coronary artery disease by FFR and angiography.

	Obstructive CAD (n = 421)	Non-obstructive CAD (n = 300)	p-value
Mean age, yrs (\pm SD)	66 \pm 11	67 \pm 11	.131
Female sex, no. (%)	109 (26%)	108 (36%)	.004
Race			
White	345 (82%)	249 (83%)	.714
Black	20 (5%)	14 (5%)	.958
Asian	44 (10%)	28 (9%)	.622
Native American	3 (1%)	2 (1%)	.942
Pacific Islander	0 (0%)	3 (1%)	–
Unknown	9 (2%)	4 (1%)	.424
Ethnicity			
Hispanic - White	93 (22%)	62 (21%)	.573
Non-Hispanic	252 (60%)	187 (62%)	.573
Indication for index FFR			
ACS	123 (29%)	41 (14%)	<0.001
Non-ACS	298 (71%)	259 (86%)	
Medical history prior to index FFR			
Any ASCVD*	270 (64%)	149 (50%)	<0.001
ACS (UA/MI)	169 (40%)	95 (32%)	.019
PCI	204 (48%)	101 (34%)	<0.001
CABG	42 (10%)	16 (5%)	.024
PAD	40 (10%)	17 (6%)	.06
TIA/CVA	46 (11%)	38 (13%)	.473
CHF	86 (20%)	71 (24%)	.299
HTN	337 (80%)	226 (75%)	.116
DM	186 (44%)	102 (34%)	.006
Dyslipidemia	337 (80%)	226 (75%)	.131
Smoking status - no. (%)			
Never smoker	212 (50%)	150 (50%)	.925
Former smoker	162 (39%)	133 (44%)	.115
Current smoker	47 (11%)	17 (6%)	.011

* Any ASCVD includes having ≥ 1 of the following: ACS (UA/MI), PCI, CABG, PAD, TIA/CVA. ACS, acute coronary syndrome, UA, unstable angina, MI, myocardial infarction, PCI, percutaneous coronary syndrome, CABG coronary artery bypass graft, PAD, peripheral arterial disease, TIA, transient ischemic attack, CVA, cerebrovascular accident, FFR, fractional flow reserve, CAD, coronary artery disease, ASCVD, atherosclerotic cardiovascular disease, CHF, congestive heart failure, HTN, hypertension, DM, diabetes mellitus.

(Table 3). There were more patients with LDL-C < 70 mg/dL in the obstructive CAD group (65% obstructive CAD vs 46% non-obstructive CAD, $p = 0.018$) at 6-months, along with a trend toward more patients with obstructive CAD vs non-obstructive CAD with LDL-C < 55 mg/dL ($p = 0.062$) (Table 4).

At 12 months, LDL-C was lower in obstructive vs non-obstructive CAD, though not statistically significant ($p = 0.104$) (Fig. 1, Table 2). In multivariable linear regression for LDL-C at 12 months, $p = ns$. Compared to those with non-obstructive CAD, the number of new statins and total statin use remained higher in the group with obstructive CAD at 12 months, but these differences were not statistically significant (Table 3). There was a greater percentage of patients with LDL-C < 70 mg/dL at 12 months in obstructive CAD vs non-obstructive CAD ($p = 0.035$) (Table 4).

The rate of high-intensity statin use was greater among those with obstructive CAD vs non-obstructive CAD at all time points ($p < 0.05$). At

baseline, 43% of individuals with obstructive CAD were taking high-intensity statin therapy, and this increased to ~60% at all follow-up time points. In the group with non-obstructive CAD, baseline high-intensity statin use was 35%, and this increased to ~50% at all follow-up time points (Table 5).

3.3. Rates of major adverse cardiovascular events (MACE) following index FFR assessment

Excluding events (e.g. PCI, MI) occurring at the time of index FFR assessment, the number of patients experiencing at least 1 MACE event (composite of CV death, MI, stroke, hospitalization for unstable angina, and revascularization (PCI or CABG)) between baseline and 12-months was greater among those with obstructive CAD (78 (18.5%)) vs non-obstructive CAD (22 (7.3%), $p < 0.001$). There was also a greater number of patients in the obstructive CAD group with ≥ 2 MACE events (16 (3.8%) vs non-obstructive CAD (4 (1.3%), $p = 0.047$). A greater number of patients in the obstructive CAD group experienced MI (obstructive CAD: 26 (6%) vs non obstructive CAD: 3 (1%) ($p < 0.001$)), hospitalization for unstable angina (obstructive CAD: 20 (5%) vs non obstructive CAD: 6 (2%) ($p = 0.050$)), and revascularization (obstructive CAD: 35 (8%) vs non obstructive CAD: 10 (3%) ($p = 0.006$)) (Table 6). Findings at index FFR predicted a greater rate of MACE (patients with ≥ 1 MACE event) in those with obstructive CAD by multivariable logistic regression in a model adjusted for age, sex, BMI, history of CHF, and history of diabetes among other variables ($p < 0.001$) (Table S3).

In summary, over 12-months following coronary angiography with FFR, patients with obstructive vs non-obstructive CAD differed in regard to intensity of lipid-lowering and MACE, but overall the entire cohort experienced only a small percent reduction in LDL-C and only a modest increase in high-intensity statin therapy (Central Figure).

4. Discussion

In this retrospective study of 721 patients undergoing evaluation by coronary angiography involving FFR, we found that an initial increase in the intensity of atherogenic lipid lowering therapy in both those with obstructive and non-obstructive CAD was not sustained beyond 3 months in those with non-obstructive CAD (FFR > 0.8 and no angiographic evidence of obstructive CAD). At 6 months, LDL-C continued to decline among those with obstructive CAD but increased (compared with levels at 3-months) among those with non-obstructive CAD. At 12 months, median LDL-C remained lower among those with obstructive vs non-obstructive CAD, though not statistically significant. High-intensity statin use was significantly greater among those with obstructive CAD at all time-points. Both those with obstructive and non-obstructive CAD were at risk for MACE at 1 year, although the risk was greater among those with obstructive CAD. Thus, our data suggest that despite persistent residual risk of MACE, those with non-obstructive CAD are treated less aggressively than those with obstructive CAD, with less intensive lipid-lowering beyond 3-months following FFR assessment. This represents a significant opportunity to change practice patterns in the treatment of patients with CAD, as following angiography involving FFR both those with obstructive and non-obstructive CAD will benefit from an intensification of atherogenic lipid-lowering therapy to reduce risk of ASCVD events.

Reducing residual ASCVD risk in this cohort could be achieved by initiation of statin therapy among the ~10–14% of patients on no statin therapy, and by transitioning patients from low- and moderate-intensity statin therapy to high-intensity statin therapy. Use of non-statin lipid-lowering therapy would likely also be effective at achieving lower atherogenic lipid levels in both groups, as for the entire cohort the rate of non-statin lipid-lowering therapy was very low: ~5–10% for ezetimibe, and ~1% for PCSK9 inhibitor monoclonal antibodies, rates that are comparable to the GOULD (Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management)

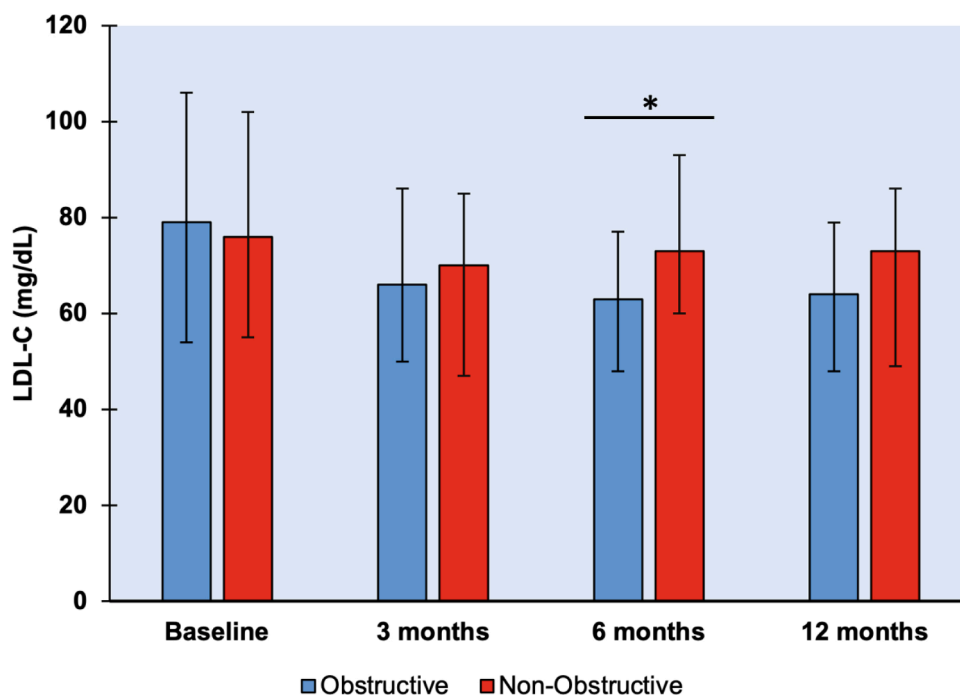


Fig. 1. LDL-C after index fractional flow reserve (FFR) assessment, comparing groups with obstructive vs non-obstructive coronary artery disease. Bars represent median (IQR) LDL-C at baseline, 3, 6, and 12 months. Compared with non-obstructive CAD, LDL-C was significantly lower in those with obstructive CAD at 6 months (* $p = 0.003$ (Mann-Whitney U test), $p = 0.001$ (multivariable linear regression)). LDL-C, low density lipoprotein cholesterol.

Table 2

LDL-C after index fractional flow reserve (FFR) assessment in obstructive vs non-obstructive coronary artery disease, including median (Q1,Q3) values at baseline, 3-, 6-, and 12-months, as well as absolute and percent change from the preceding time point.

	Obstructive CAD		Non-Obstructive CAD		p-value*
LDL-C (mg/dL)					
Baseline	79 (54,106) (n = 288)	-	76 (55,102) (n = 199)	-	.494
3 mo.	66 (50,86) (n = 120)	-13 (-16%)	70 (47,85) (n = 60)	-6 (-8%)	.926
6 mo.	63 (48,77) (n = 102)	-3 (-5%)	73 (60,93) (n = 63)	3 (+4%)	.003
12 mo.	64 (48,79) (n = 151)	1 (+2%)	73 (49,86) (n = 80)	0 (+0%)	.104

* Between group comparison of LDL-C values at each time point using Mann Whitney U test. LDL-C, low density lipoprotein cholesterol, CAD, coronary artery disease.

registry with regard to ezetimibe but lower with regard to PCSK9 inhibitors [6]. We also observed a greater percentage of women in the non-obstructive CAD group vs obstructive CAD group, a pattern which has been observed previously and could result in under treatment of women with non-obstructive CAD who remain at risk for cardiovascular events [19].

In contrast to our finding that lower atherogenic lipids and intensification of lipid-lowering therapy appears to wane at 6-months in those with non-obstructive CAD, in the FAME2 registry cohort of participants with FFR > 0.8, statin therapy increased from 77% at baseline, to > 90%

for up to 2 years [5]. Optimal medical therapy in FAME2 (including the FAME2 registry) included atorvastatin 20 to 80 mg daily, or another similar statin with or without ezetimibe in order to reduce LDL-C to < 70 mg/dL [20]. In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, medical therapy included using an LDL-C goal of < 70 mg/dL by using high-intensity statin therapy, as well as ezetimibe or evolocumab if needed to reach LDL-C goal. By the end of the trial, median LDL-C in both invasive and conservative groups was reduced from 83 to 64 mg/dL. Use of any statin was high (~94–95% in all groups both at baseline and last visit), but the use of high-intensity statin therapy and ezetimibe increased between baseline and last visit in both groups from ~41% to ~66% and from ~4% to 24%, respectively [21]. The difference between our findings and those of FAME2 and ISCHEMIA is likely explained by our use of a real-world cohort, in which healthcare professionals are not provided with guidance on optimal medical therapy within the framework of a clinical trial.

Similar to our findings, a single-center study which examined treatment patterns and event rates among a cohort of patients with FFR > 0.8 found that in 192 patients over a median of 2.8 years of follow-up, 31.8% were treated to LDL-C < 70 mg/dL and 68.2% had LDL > 70 mg/dL. Statin use at discharge was higher among those with LDL-C < 70 mg/dL (93.4% vs 81.7%, $p = 0.032$), and a similar trend toward higher statin use was seen at the time of last follow-up among those with LDL-C < 70 mg/dL (91.8% vs 80.9%, $p = 0.053$). Interestingly, there was a greater rate of deferred lesion failure (defined as either deferred lesion revascularization or deferred vessel MI) among those with LDL-C > 70 mg/dL [22]. In contrast to these findings we observed a loss of initial intensification of therapy over time among those with FFR > 0.8. Other cohort studies have described lower rates of medical therapy in non-obstructive CAD. For example, among 1088 patients in British Columbia with stable angina and non-obstructive CAD (defined by estimation during angiography), statin use was only 59% at 3 months follow-up [23].

Despite the differences we observed between obstructive and non-obstructive CAD groups, it is important to acknowledge that atherogenic lipids were quite low and lipid-lowering therapy was overall fairly

Table 3
Lipid-lowering therapy over 12 months following index FFR assessment in obstructive vs non-obstructive CAD.

	Obstructive CAD (n = 421)		Non-obstructive CAD (n = 300)		p-value (New Rx)	p-value (Total Rx)
	New Rx	Total (%) on Rx	New Rx	Total (%) on Rx		
Baseline						
Statin	–	324 (77%)	–	218 (73%)	–	.188
Ezetimibe	–	18 (4%)	–	17 (6%)	–	.392
Alirocumab	–	1 (0.2%)	–	0	–	1
Evolocumab	–	3 (1%)	–	0	–	.270
Fish Oil	–	57 (13.5%)	–	36 (12%)	–	.543
Fibrate	–	13 (3%)	–	11 (4%)	–	.669
Other LLT*	–	9 (2%)	–	14 (5%)	–	.057
3 mo.						
		n = 339		n = 250		
Statin	48	312 (92%)	39	215 (86%)	.626	.018
Ezetimibe	4	17 (5%)	2	19 (8%)	.650	.195
Alirocumab	0	2 (1%)	0	0	–	–
Evolocumab	3	4 (1%)	0	1 (0.4%)	–	.307
Fish Oil	7	45 (13.3%)	5	31 (12.4%)	.956	.754
Fibrate	0	8 (2%)	0	5 (2%)	–	.768
Other LLT*	2	12 (4%)	2	10 (4%)	.759	.771
6 mo.						
		n = 303		n = 228		
Statin	21	276 (91%)	8	195 (86%)	.086	.045
Ezetimibe	1	15 (5%)	3	19 (8%)	.193	.115
Alirocumab	2	3 (1%)	1	1 (0.4%)	.736	.467
Evolocumab	1	4 (1%)	1	1 (0.4%)	.840	.298
Fish Oil	1	41 (13.5%)	1	28 (12.3%)	.840	.671
Fibrate	0	7 (2%)	1	5 (2%)	–	.928
Other LLT*	1	10 (3%)	1	11 (5%)	.840	.372
12 mo.						
		n = 299		n = 206		
Statin	10	272 (91%)	6	178 (86%)	.785	.107
Ezetimibe	4	21 (7%)	0	18 (9%)	–	.478
Alirocumab	1	4 (1%)	3	3 (1%)	.162	.911
Evolocumab	1	4 (1%)	2	2 (1%)	.360	.708
Fish Oil	9	44 (14.7%)	0	28 (13.6%)	–	.723
Fibrate	1	7 (2%)	0	6 (3%)	–	.690
Other LLT*	2	6 (2%)	2	6 (3%)	.706	.511

*Other LLT: niacin, bile acid sequestrants, red yeast rice, berberine, plant sterol/stanol, fenugreek, bempedoic acid. FFR, fractional flow reserve, CAD, coronary artery disease, LLT, lipid lowering therapy.

Table 4
Number (percent) of patients with obstructive vs. non-obstructive CAD reaching guideline directed LDL-C targets over time following index FFR assessment.

	Obstructive CAD	Non-Obstructive CAD	p-value
Baseline			
LDL-C < 55 mg/dL	73/288 (25%)	46/199 (23%)	.573
LDL-C < 70 mg/dL	120/288 (42%)	84/199 (42%)	.905
3 mo.			
LDL-C < 55 mg/dL	38/120 (32%)	21/60 (35%)	.653
LDL-C < 70 mg/dL	68/120 (57%)	29/60 (48%)	.290
6 mo.			
LDL-C < 55 mg/dL	33/102 (32%)	12/63 (19%)	.062
LDL-C < 70 mg/dL	66/102 (65%)	29/63 (46%)	.018
12 mo.			
LDL-C < 55 mg/dL	52/151 (34%)	23/80 (29%)	.380
LDL-C < 70 mg/dL	88/151 (58%)	35/80 (44%)	.035

CAD, coronary artery disease, FFR, fractional flow reserve, LDL-C, low density lipoprotein cholesterol.

high among those with non-obstructive CAD, including at baseline, with 73% of patients receiving statin therapy. This rate of statin utilization among individuals with non-obstructive CAD is similar to the rate of statin utilization (77.8%) seen among patients with obstructive coronary artery disease in the PINNACLE (Practice Innovation and Clinical Excellence) registry [15]. It is possible that this is a result of selection

bias in our study design, in that all patients in this study had been referred for coronary angiography, thus reflecting that this cohort was already perceived by treating clinicians to be at high enough risk of cardiovascular events to warrant further evaluation by angiography. Indeed, 50% of the patients in the group found to have non-obstructive CAD on their index angiogram and FFR assessment had a history of prior ASCVD and our obstructive CAD cohort was particularly high-risk, considering that 29% of all index angiograms and FFR measurements in this group occurred in the setting of ACS. Another high-risk feature of our cohort is that 18.5% (obstructive CAD) and 7.3% (non-obstructive CAD) of patients experienced at least 1 MACE event by 1 year follow-up. Therefore, despite relatively lower atherogenic lipids at baseline, even more aggressive lipid-lowering therapy might be beneficial in both those with obstructive and non-obstructive CAD in this cohort. Finally, that this study included only patients from an academic center may have also contributed to more aggressive atherogenic lipid management, as seen in the GOULD registry [6].

Study limitations include being a single-center, retrospective study with data derived from the EHR, with loss of patient follow-up over time. Limitations related to sample size likely explain the discrepancy we observed when comparing median LDL-C between obstructive and non-obstructive CAD groups at 12 months, and assessing for the effect of group status on LDL-C at 12 months using multivariable linear regression. Our study design also results in selection for those patients who were being actively followed over the 12 months after their index FFR assessment, including with follow-up lipid testing. Also, we did not independently adjudicate use of lipid-lowering therapies or MACE events, as for these measures we relied on the accuracy and completeness of the data entered by healthcare professionals into the EHR. We used the prescription of lipid-lowering therapies as our measure of lipid-lowering therapy use, which does not capture patient adherence to these

Table 5

Rates of high-intensity statin use vs moderate-intensity statin, low-intensity statin, or no statin use among those with obstructive vs non-obstructive CAD at baseline, 3, 6, and 12 months after index FFR assessment.

	Obstructive CAD			Non-Obstructive CAD			p-value
	High-Intensity (n = 421)	Low to Moderate-Intensity	No Statin	High-Intensity (n = 300)	Low to Moderate-Intensity	No Statin	
Baseline	181 (43.0%)	142 (33.7%)	98 (23.3%)	106 (35.3%)	112 (37.3%)	82 (27.3%)	.038
3 mo.	214 (63.1%) (n = 339)	98 (28.9%)	27 (8.0%)	126 (50.4%) (n = 250)	89 (35.6%)	35 (14%)	.002
6 mo.	181 (59.7%) (n = 303)	96 (31.7%)	26 (8.6%)	108 (47.4%) (n = 228)	87 (38.2%)	33 (14.5%)	.005
12 mo.	180 (60.2%) (n = 299)	92 (30.8%)	27 (9.0%)	103 (50%) (n = 206)	75 (36.4%)	28 (13.6%)	.023

High intensity: atorvastatin 40–80 mg or rosuvastatin 20–40 mg. Low to moderate-intensity: atorvastatin <40 mg, rosuvastatin <20 mg, simvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin. CAD, coronary artery disease, FFR, fractional flow reserve.

Table 6

Number of patients with MACE between baseline and 12-months after FFR assessment comparing those with obstructive vs non-obstructive CAD.

	Obstructive CAD (n = 421)	Non-obstructive CAD (n = 300)	p-value
Patients with ≥ 1 MACE event*	78 (18.5%)	22 (7.3%)	<0.001
Patients with ≥ 2 MACE events	16 (3.8%)	4 (1.3%)	.047
CV Death	8 (1.9%)	4 (1.3%)	.769
MI	26 (6.2%)	3 (1%)	<0.001
Stroke	4 (1%)	2 (0.7%)	1
Hospitalization for UA	20 (4.8%)	6 (2%)	.050
Revascularization (PCI or CABG)	35 (8.3%)	10 (3.3%)	.006
PCI	31 (7.4%)	7 (2.3%)	.003
CABG	4 (1%)	3 (1%)	.946

* MACE events exclude those occurring at the time of index FFR assessment. MACE events include: CV death, MI, stroke, hospitalization for unstable angina, revascularization (PCI or CABG). MACE, major adverse cardiovascular events, CV, cardiovascular, MI, myocardial infarction, UA, unstable angina, PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting.

therapy appears to wane by 6 months among those with non-obstructive CAD and both those with obstructive and non-obstructive disease remain at risk for MACE events at 1 year. After an FFR assessment, patients with non-obstructive CAD may benefit from more persistent attention to lipid-lowering therapies to reduce residual ASCVD risk.

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Declaration of interests

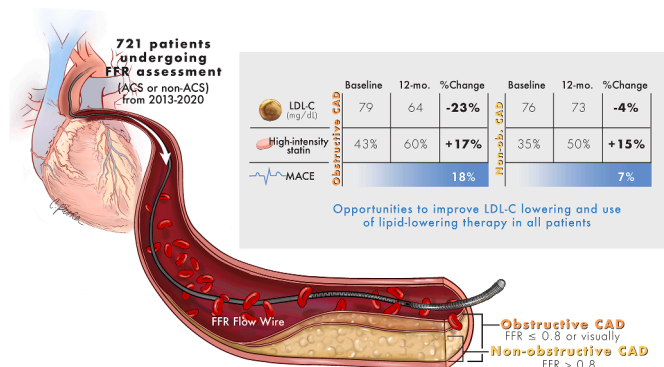
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100473.

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Central Figure. Following coronary angiography with fractional flow reserve (FFR), those with non-obstructive CAD (vs obstructive CAD) receive less intensive lipid-lowering therapy to lower LDL-C. However, intensification of LDL-C lowering is modest in both groups, and all remain at risk for MACE over 12-months. Therefore, following coronary angiography with FFR, all patients will benefit from greater intensification of lipid-lowering therapy.

medications. Our study should be replicated using a larger sample size, with data from multiple institutions, in order to further assess these treatment patterns.

In conclusion, our findings suggest that after angiography and an FFR measurement, there may be more focus on intensifying medical therapy during the first 3 months of follow-up, as the “spotlight” has been placed on these patients. However, this attention to intensifying medical

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