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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Longitudinal Control of Lipid Levels in Patients With Premature Coronary Artery Disease

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ABSTRACT

BACKGROUND Lipid-lowering therapy (LLT) is a central aspect of the treatment of patients with coronary artery disease (CAD), and the benefits of LLT accrue over time. However, there are limited real-world data on longitudinal lipid control in patients with premature CAD.

OBJECTIVES The purpose of this study was to assess longitudinal attainment of guideline-recommended lipid goals and outcomes in a contemporary cohort of patients with premature CAD.

METHODS We enrolled males younger than 50 years and females younger than 55 years with coronary stenosis of >50% and examined achievement of lipid goals, LLT characteristics, and cardiovascular outcomes (major adverse cardiovascular event [MACE]).

RESULTS Of 476 patients who presented with acute coronary syndrome (ST-elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina) (68%), stable angina (28%), or other symptoms, 73.2% achieved low-density lipoprotein cholesterol (LDL-C) <1.8 mmol/L on at least 1 occasion, but only 27.3% consistently stayed in the target range for 3 years after diagnosis. Although 73.9% of patients received high-intensity LLT at the time of diagnosis, only 43.5% had good adherence over the following 3 years. In multivariable analysis, 1 mmol/L increase in time-weighted average exposure to LDL-C, but not the lowest achieved LDL-C, was associated with a higher risk of MACE, hazard ratio 2.02 (95% CI: 1.48-2.76), when adjusted for sex, age, hypertension, diabetes, and smoking.

CONCLUSIONS We found low rates of longitudinal lipid target achievement in patients with premature CAD. Cumulative LDL-C exposure, but not lowest achieved LDL-C, was associated with risk of MACE. This highlights the critical importance of longitudinal control of lipids levels and identifies opportunities to improve LLT and maximize the time-dependent benefits of lipid-lowering. (JACC Adv 2023;2:100696) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/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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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering therapy

MACE = major adverse cardiovascular event

PDC = proportion of days covered

TWE-LDL-C = time-weighted average exposure to LDL-C

Despite improvements in primary and secondary prevention, rates of premature coronary artery disease (CAD) have remained stagnant.[1,2] Premature CAD is an important public health issue due to the potential loss of lifetime productivity, increased utilization of healthcare resources, and the need to cope with the burden of disease for several decades of life.[3-6]

Elevated levels of apolipoprotein B-containing lipoproteins including low-density lipoprotein (LDL) are causal for CAD[7] via their role in atherosclerotic plaque formation, and lowering blood lipids is key to reducing cardiovascular risk in primary and secondary prevention settings. Multiple studies and meta-analyses conducted by the Cholesterol Treatment Trialists' collaboration have demonstrated that the reduction of cardiovascular risk is dose- and time-dependant.[8-12] Greater benefits are achieved with larger absolute reductions in LDL cholesterol (LDL-C) levels.[8,9] In randomized trials of statin therapy, after the first year of treatment, every 1 mmol/L reduction in LDL-C was associated with a ~21% proportional risk reduction in major cardiovascular events.[8,9] The proportional risk reduction is smaller during the first year of treatment (termed a lag effect), subsequently increases, and persists beyond the end of randomized trials (termed a legacy effect).[10-12] Consequently, the absolute benefits of lipid lowering increase with increased duration of treatment.[8-12]

Reflecting this evidence, current guidelines on cardiovascular prevention have introduced more stringent lipid targets in secondary prevention.[13-15] To achieve this, high-intensity statins at the highest-tolerated dose are recommended for all patients with CAD, and for patients who do not reach treatment goals, more intensive lipid lowering with the addition of non-statin therapies is recommended.[13-15]

Previous studies of lipid-lowering therapy (LLT) and attainment of treatment goals reported undertreatment and low rates of lipid target achievement in secondary prevention of CAD.[16-22] However, these studies often employed cross-sectional designs or short-term assessments that did not allow for assessment of visit-to-visit variability and longitudinal control of lipid levels. In addition, most studies either used prescription records and assumed sufficient adherence or self-reported information, so opportunities to estimate the role of adherence in target nonachievement were limited. Finally, no studies have reported longitudinal target achievement and cardiovascular outcomes in patients with premature CAD. Cardiovascular prevention in younger patients is an important and challenging issue because of the need for these patients to take preventive medications for several decades, and higher rates of medication nonadherence has been previously observed in younger patients than in older age groups.[23-25] Additionally, inherited dyslipidemias such as familial hypercholesterolemia are more prevalent in patients with premature CAD than in older patients.[26,27]

The objectives of this study were therefore to 1) longitudinally assess lipid-lowering treatment and achievement of guideline-recommended lipid targets; 2) explore the role of treatment adherence in target nonachievement; and 3) evaluate the consequences of target nonachievement in a contemporary cohort of patients with premature CAD.

METHODS

STUDY POPULATION AND DATA COLLECTION. We enrolled patients with a diagnosis of CAD (referred to hereafter as the index event) at the age of ≤50 years in males and ≤55 years in females on the basis of angiographically confirmed stenosis of ≥50% in ≥1 epicardial artery or coronary revascularization. Patients were recruited from 2016 to 2021 (Supplemental Figure 1). Patients with data available for at least 1 year after presentation were included. The distribution of patients by available follow-up time is summarized in Supplemental Table 1. Clinical information, medication dispensation records, and laboratory values were collected from questionnaires, physician notes, electronic medical records, and province-wide pharmacy network records.[28] At enrollment, information was collected for all patients for the period starting from 3 years prior to the index event to establish baseline laboratory values as well as presence of cardiovascular risk factors, comorbidities, and inherited dyslipidemias. Diagnosis, burden of the disease, and management at presentation were confirmed with reports from Cardiac Services of British Columbia Registry, an electronic information system containing information on all patients who receive cardiac procedures in the province.[29] Date of the index event was defined as the study start date. To address the study objectives, information about treatment, outcomes, and laboratory values was collected by study coordinators on seasonal basis starting from the start date and transferred to the SAVE BC study database. Patients were treated according to local standards of care. Lipid assays were performed at clinical laboratories as part of routine

clinical care. Highest lipid values measured before or at the time of presentation with CAD were defined as baseline.

CARDIOVASCULAR RISK FACTORS AND INHERITED DYSLIPIDEMIAS. Definitions of cardiovascular risk factors and methods of assessment of diet and physical activity are listed in the Supplemental Methods and described elsewhere.[30] The presence of familial hypercholesterolemia was assessed with Dutch Lipid Clinic Network criteria using pre-treatment lipid values.[31] For patients without pre-treatment data available (11% of the study cohort), LDL-C levels were imputed according to the lipid-lowering medication and dose.[32]

LLT AND TREATMENT TARGETS. Treatment was determined based on pharmacy dispensation records. Adherence to LLT was assessed using the proportion of days covered (PDC).[33,34] In the case of combined therapy, the number of days covered was calculated as the number of days when at least 1 of the medications was in possession for the period of a combined therapy (Supplemental Methods). This approach was also used to assess adherence to antihypertensive and hypoglycemic medications (Supplemental Methods). Finally, adherence was separately assessed for statins, ezetimibe, and treatment with PCSK9 monoclonal antibodies. Adherence was defined as optimal if PDC was ≥80%, suboptimal if PDC was 40% to 79%, and low if PDC was <40%. The absence of the records during a year was classified as a discontinuation for the year. Treatment intensity classification is presented in the Supplemental Table 2.

TREATMENT GOALS. Treatment goals were defined as LDL-C <1.8 mmol/L (70 mg/dL) and non-high-density lipoprotein cholesterol (HDL-C) <2.4 mmol/L (92 mg/dL), in accordance with current national guidelines.[13] The proportion of lipid values in the goal ranges was calculated separately for the periods of 1, 2, and 3 years after presentation for patients with ≥2 values available for the period. The proportion equal to 1.0 was defined as being consistently at target. To assess longitudinal goal achievement, time-weighted average exposure to LDL-C (TWE-LDL-C) was calculated for the periods of 1, 2, and 3 years after presentation for all patients with baseline values and ≥1 value available for every year withing assessed time period.[35,36] Availability of lipid values is summarized in Supplemental Figure 2. Cumulative exposure to LDL-C was calculated as the area under LDL-C vs years after presentation curve, starting from the LDL-C value measured at Index event and expressed in mmol/L × years. For patients with multiple measurements within years, averaged values for every year were used in the calculations. TWE-LDL-C was calculated as a cumulative LDL-C divided by a total length of the period.

CARDIOVASCULAR OUTCOMES. Recurrent major adverse cardiovascular events (MACEs) were defined as death, recurrent myocardial infarction (MI), coronary revascularization performed later than 90 days after the index event, or unstable angina requiring invasive angiography.

STATISTICAL ANALYSIS. Analyses were performed using IBM SPSS Statistics v28.0 and Rstudio v1.1.456. Categorical variables were summarized as frequencies and proportions and compared with chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean ± SD or median (Q1-Q3) and compared with analysis of variance or Kruskal-Wallis tests, as appropriate. A 2-tailed value of $P < 0.05$ was considered statistically significant. No adjustments were made for multiple comparisons. The association of lipid target achievement and outcomes was assessed with multivariable Cox regression analysis. TWE-LDL-C was calculated for every patient up to the time of outcome or the end of the available follow-up period. The model included age at presentation, sex, presentation with acute coronary syndrome vs not, and major cardiovascular risk factors including hypertension, diabetes, and continuing smoking regardless of their statistical significance because of their clinical significance in the context of cardiovascular outcomes. Proportional-hazards assumption for TWE-LDL-C and lowest achieved LDL-C was tested in a time-dependent Cox model and by using Schoenfeld residuals. To examine robustness of the finding and to account for the influence of the baseline LDL-C levels on the TWE-LDL-C and the lowest achieved LDL-C, a sensitivity analysis was performed where the model was additionally adjusted for the baseline LDL-C level. Unadjusted rates of cardiovascular outcomes were reported as proportions and compared between patients with TWE-LDL-C at target vs not. No imputations were performed for missing data.

ETHICS. The study was approved by the Providence Health Care Research Ethics Board, certificate number H20 to 00758. All participants provided written informed consent.

RESULTS

In total, 476 patients (27.3% female) with premature obstructive CAD were included in the analysis (Supplemental Figure 1). Of them, 68% presented

TABLE 1 Demographics, Cardiovascular Risk, and Characteristics at Presentation

Presentation/reason for referral for coronary angiography	
STEMI	102 (21.4%)
NSTEMI	176 (37.0%)
Unstable angina	59 (12.4%)
Stable angina	123 (25.8%)
Other	16 (3.4%)
Number of vessels with stenosis >50%	
1	206 (43.2%)
2	148 (31.1%)
3	122 (25.7%)
Management at presentation	
Angiography only	82 (17.2%)
PCI	293 (61.5%)
CABG	102 (21.4%)
Demographics and lifestyle	
Age at presentation, y	46.4 ± 5.2
Female	130 (27.3%)
Ethnicity (N = 329)	
Caucasian	161 (48.9%)
East Asian	41 (12.5%)
South/West Asian	75 (27.3%)
Native North American	11 (3.3%)
Others	41 (13.4%)
Educational level (N = 326)	
Less than high school	17 (5.2%)
High school	68 (20.9%)
Trades certificate	10 (3.1%)
College or diploma	60 (18.4%)
University	171 (52.4%)
Lifestyle at baseline (N = 305)	
Moderate/high level of physical activity	199 (65.2%)
Daily consumptions of fruit or vegetables	248 (84.9%)
Daily consumption of salty food or snacks	180 (62.1%)
Deep fried food, fast food, or snacks ≥3 times per week	135 (46.4%)
Meat or poultry ≥2 times per day	164 (56.2%)
Cardiovascular risk factors	
Hypertension	217 (46.1%)
Diabetes	128 (27.3%)
Obesity (BMI ≥30 kg/m^2)	195 (41.0%)
Dyslipidemia	355 (75.7%)
Smoking	
At presentation with CAD	117 (25.7%)
After presentation with CAD	64 (14.0%)
Ever	242 (50.8%)
Family history of premature CVD (N = 313)	123 (39.3%)

Continued on the next page

with acute coronary syndrome (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina), and the remainder with stable angina (28%) or other symptoms. Patient demographics, cardiovascular risk factors, baseline lipid values, and characteristics at presentation are shown in **Table 1**. The most prevalent major cardiovascular risk factors were dyslipidemia (75.7%) and hypertension (46.1%). Diabetes was present in 27.3% of the cohort. When assessed with Dutch Lipid Clinic Network criteria, 12.6% of patients had definite or probable familial hypercholesterolemia, and 57.4% had possible familial hypercholesterolemia. In addition, 36% of patients had Lp(a) ≥500 mg/L. Detailed information on other comorbidities and baseline laboratory values is presented in Supplemental Table 4.

USE OF LLT. **Figure 1** summarizes LLT use over 3 years after index presentation. In the first year, 64.6% of patients received high-intensity statins, and 9.3% received a combination therapy with high-intensity statins and either ezetimibe or a PCSK9 inhibitor. By the end of the third year, the proportion of patients on monotherapy with high-intensity statins decreased to 47.1%, and the proportion who received combination LLT increased to 18.7%. At the same time, the proportion of patients with good adherence decreased from 69.5% to 43.5%, and 17.9% of patients permanently discontinued treatment including 7.1% who never filled a prescription for LLT (**Central Illustration**). We did not observe any significant differences in adherence between patients receiving different combinations of LLT or between patients with different diagnoses at presentation with CAD (Supplemental Tables 5 and 6). When analyzed separately, we observed numerically higher adherence and lower rates of discontinuation for ezetimibe and anti-PSCK9 monoclonal antibodies than statins which were not statistically significant (Supplemental Table 7). We also observed better adherence to antihypertensive and hypoglycemic medications than LLT (Supplemental Table 8).

ATTAINMENT OF TREATMENT TARGETS. **Figure 2**, **Table 2**, and Supplemental Figure 3 summarize the attainment of lipid goals. During the first year of treatment, 73.2% of patients had at least 1 LDL-C value lower than 1.8 mmol/L, and 66.1% had at least 1 non-HDL-C lower than 2.4 mmol/L. In 75.4% of patients, LDL-C decreased by ≥50% from the highest baseline value. However, the proportion of patients with LDL-C values consistently in the target range was 38.9%, 31.0%, and 27.3% during year 1, 2, and 3 after presentation with CAD, respectively. The corresponding percentages with non-HDL-C <2.4 mmol/L were 34.6%, 27.5%, and 25.1%. TWE-LDL-C calculated for the same periods was <1.8 mmol/L in 32.4%, 46.6%, and 50.3% of patients, respectively, reflecting the influence of the first LDL-C measurement recorded at the index event prior to treatment initiation or intensification and time required for a decrease in LDL-C. Even among patients who achieved their LDL-C goal at least once during the first year of treatment, more than one-third had an average

exposure to LDL-C higher than the recommended threshold.

ROLE OF LLT TYPE AND ADHERENCE IN TARGET ACHIEVEMENT. Patients with higher baseline LDL-C were more likely to receive a combination of high-intensity statins with ezetimibe or anti-PCSK9 monoclonal antibodies (Supplemental Table 9). Compared to patients who received monotherapy with statins, these patients had a larger absolute reduction and comparable proportional reduction in LDL-C. However, they were no more successful in achieving longitudinal treatment targets. Patients with high adherence were numerically more likely than those with suboptimal or low adherence to reach the LDL-C target (77.4% vs 71.2% and 61.9%, $P = 0.08$) and were more likely to consistently stay at target over the period of 2 (36.0% vs 25.6% and 13.6%, $P = 0.006$) and 3 years after presentation (32.5% vs 22.6% and 12.8%, $P = 0.013$). (**Table 2**). Patients with high adherence were also more likely than those with suboptimal or low adherence to have TWE-LDL-C at target during 2 (53.9% vs 36.4%, 27.3%, $P < 0.001$) and 3 (56.7% vs 46.1%, 24.0%, $P = 0.005$) years after presentation. Similar trends were observed for the non-HDL-C target (**Table 2**).

ASSOCIATION OF TARGET ACHIEVEMENT WITH CARDIOVASCULAR OUTCOMES. After a mean follow-up of 3.7 years, 74 (15.5%) patients experienced MACE (**Central Illustration**). Among them, 7 (1.5%) patients died, 26 (5.5%) had a non-fatal MI, 21 (4.2%) had angina requiring recurrent revascularization, and 22 (4.6%) had recurrent unstable angina requiring cardiac catheterization. Patients who experienced recurrent MACE had higher TWE-LDL-C for the period between index presentation and recurrence or end of follow-up: 2.28 (0.93) mmol/L/year vs 1.88 (0.62) observed in those without recurrent MACE ($P < 0.001$). In contrast, the mean lowest achieved LDL-C was similar between individuals who did or did not experience a recurrent MACE, 1.58 (0.76) vs 1.56 (0.76) mmol/L ($P = 0.80$). Recurrent MACE occurred in 24.0% of patients with TWE-LDL ≥1.8 mmol/L and 13.1% of patients with TWE-LDL-C <1.8 mmol/L ($P = 0.009$) (**Figure 3**, Supplemental Figure 4). Among the components of the composite MACE endpoint, non-fatal MI occurred significantly more frequently in individuals with TWE-LDL ≥1.8 mmol/L (10.6%) than in those with TWE-LDL-C <1.8 mmol/L (3.4%, $P = 0.014$) (**Figure 3**).

TABLE 1 Continued

Previously diagnosed	
Myocardial infarction	31 (9.4%)
Peripheral artery disease	8 (2.5%)
Cerebrovascular disease	8 (2.4%)
Chronic kidney disease	8 (2.4%)
Female-specific risk factors (N = 130)	
Gestational diabetes	20 (25.3%)
Gestational hypertension	12 (15.4%)
Pre-eclampsia	4 (5.1%)
Highest baseline lipid values	
Total cholesterol, mmol/L (mg/dL)	5.9 ± 1.7 (128 ± 66)
LDL-C, mmol/L (mg/dL)	3.8 ± 1.5 (147 ± 58)
Non-HDL-C, mmol/L (mg/dL)	5.0 ± 1.6 (193 ± 62)
HDL-C, mmol/L (mg/dL)	1.3 ± 0.4 (50 ± 15)
Triglycerides, mmol/L (mg/dL) (N = 417)	2.3 (1.5-3.5) (204 [133-310])
Lp(a), mg/L (N = 255)	283 (112-832)
Apolipoprotein B, g/L (N = 314)	1.2 ± 0.4
Number of available follow-up lipid values	
LDL-C measurements per patient, range	4 (3-6), 1-17
Non-HDL-C measurements per patient, range	4 (2-5), 1-17

Values are n (%), mean ± SD, or median (IQR).

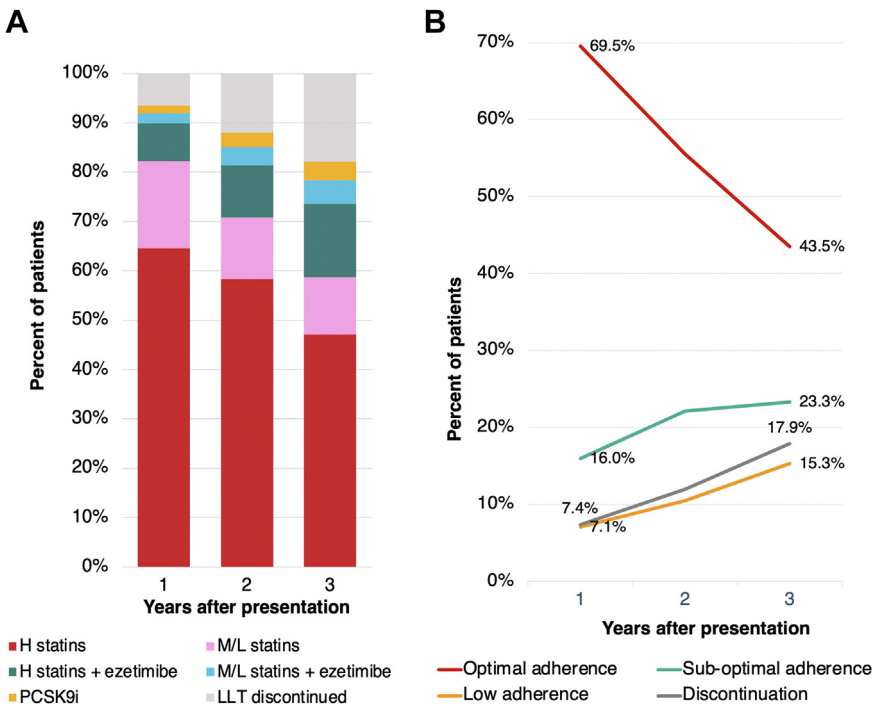
BMI = body mass index; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

In multivariable Cox regression, when adjusted for sex, age at presentation, acuity at presentation, hypertension, diabetes, and continued smoking, each 1-mmol/L increase in the TWE-LDL-C was associated with an increased risk of MACE with a HR of 2.02 (95% CI: 1.48-2.76, $P < 0.001$). In contrast, the lowest achieved LDL-C was not associated with MACE when adjusted for the same parameters, (HR: 0.89, 95% CI: 0.58-1.68, $P = 0.60$). In time-dependent Cox model, there were no significant time effects identified for TWE-LDL-C (P for interaction = 0.09) and lowest achieved LDL (P for interaction 0.31). In the sensitivity analysis model additionally adjusted for baseline LDL-C, corresponding values of HR were 2.54 (95% CI: 1.72-3.77) for TWE-LDL-C and 1.12 (95% CI: 0.74-1.69) for the lowest achieved LDL-C.

DISCUSSION

This is the first real-world observational study examining longitudinal rates of lipid target attainment in a population of patients with premature CAD. The major findings of this study are that while nearly three-quarters of patients had lipid levels in the target range at a single time point, less than one-third of patients consistently stayed in the target range during 3 years after presentation. Lipid goal non-attainment was associated with decreasing adherence over time. Poorer cumulative LDL-C control, but not

FIGURE 1 Lipid-Lowering Therapy and Adherence to Treatment Over 3 Years After Presentation With Premature Coronary Artery Disease



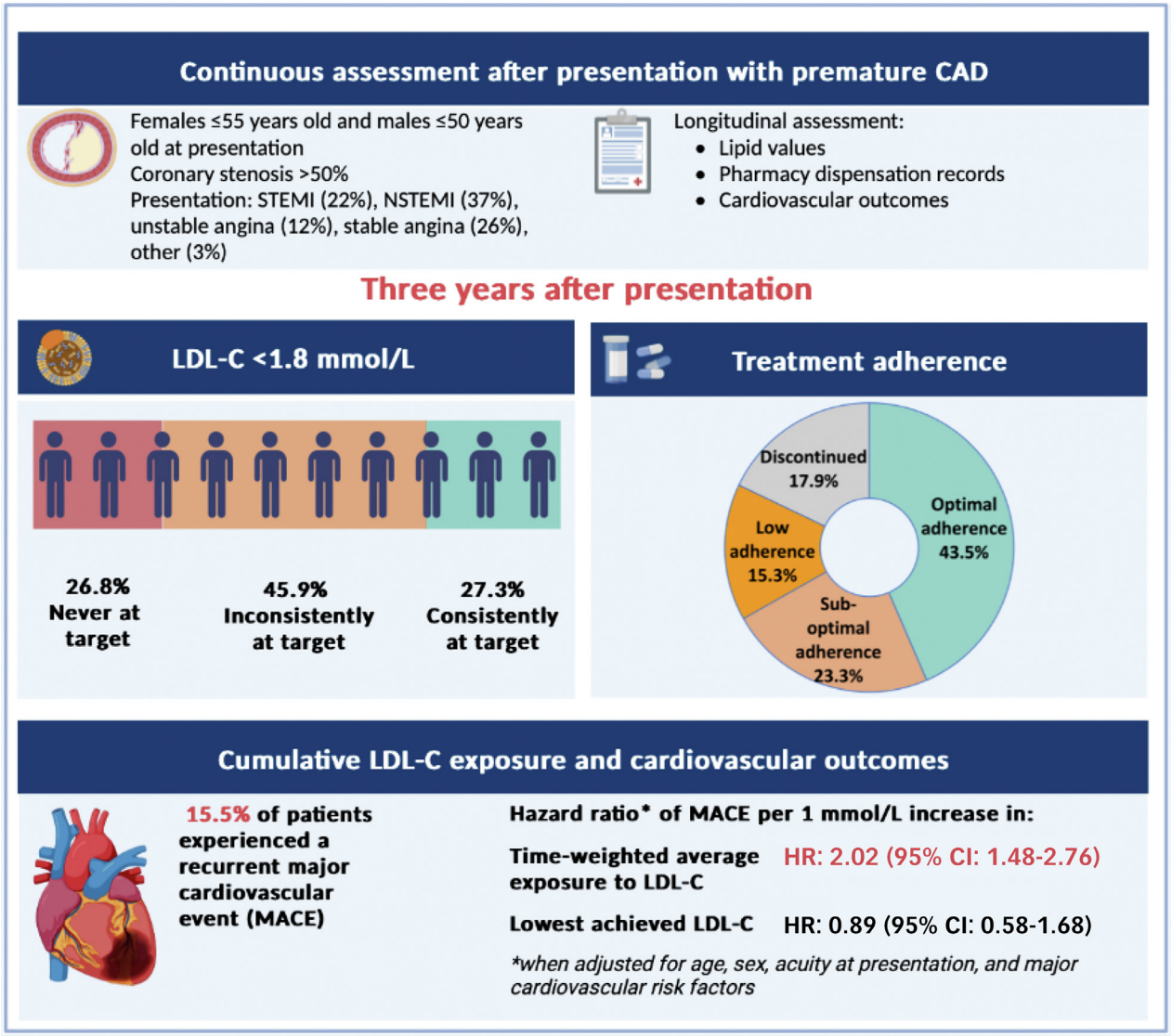
Lipid-lowering therapy (A) and adherence to treatment (B). In the 3 years after presentation, proportion of patients receiving monotherapy with high intensity stating decreased from 64.6% to 47.1% while the proportion of those who received a combined therapy or anti-PCSK9 antibody therapy increased from 9.3% to 18.7%. The proportion of patients with good adherence decreased from 69.5% in the first year to 43.5% in the third year; 7.1% of patients never filled prescriptions for lipid-lowering medications (primary nonadherence) and additional 10.8% permanently discontinued treatment during the 3 years. H statins = high-intensity statins; LLT = lipid-lowering therapy; M/L statins = medium- or low-intensity statins; PCSK9i = therapy with monoclonal antibodies targeted against the proprotein convertase subtilisin kexin type 9.

the lowest achieved LDL-C, was associated with an increased risk of recurrent MACE.

ATTAINMENT OF TREATMENT TARGETS. Previous studies that employed cross-sectional designs or short-term assessment periods reported rates of 36% to 67% for achieving LDL-C <1.8 mmol/L in secondary prevention or high-risk cohorts.[16-19] Consistent with this, we found that 73.2% of patients achieved an LDL-C <1.8 mmol/L on at least 1 occasion in the first year after presentation. In contrast, we observed that only 27.3% consistently stayed in the goal range of LDL-C over a 3-year period. This indicates that while most patients can achieve recommended lipid goals temporarily, only a small minority can consistently maintain these lipid levels. This has implications for treatment strategies, as it suggests that the primary barrier that must be overcome is to develop treatment approaches that optimize long-term tolerability and adherence. This further highlights the importance of a longitudinal approach when assessing the success of treatment goals in research and clinical settings, as cross-sectional or short-term approaches may lead to overestimation of treatment success.

LONGITUDINAL APPROACH TO LIPID CONTROL. We used the TWE-LDL-C to evaluate the success of lipid treatment in a secondary prevention setting. There is compelling evidence that the beneficial effects of lipid-lowering on cardiovascular risk are cumulative over time.[8-12] Zhang et al[36] observed an association between TWE LDL-C, calculated using imputed LDL-C values, and incident CAD in young and middle-aged adults. In our study, we used LDL-C values obtained as a part of standard-of-care management of patients with premature obstructive CAD and observed that the TWE-LDL-C, but not the lowest achieved LDL-C, was associated with increased risk of recurrent MACE. Our

CENTRAL ILLUSTRATION **Longitudinal Control of Lipid Levels and Cardiovascular Outcomes in Patient With Premature Coronary Artery Disease**



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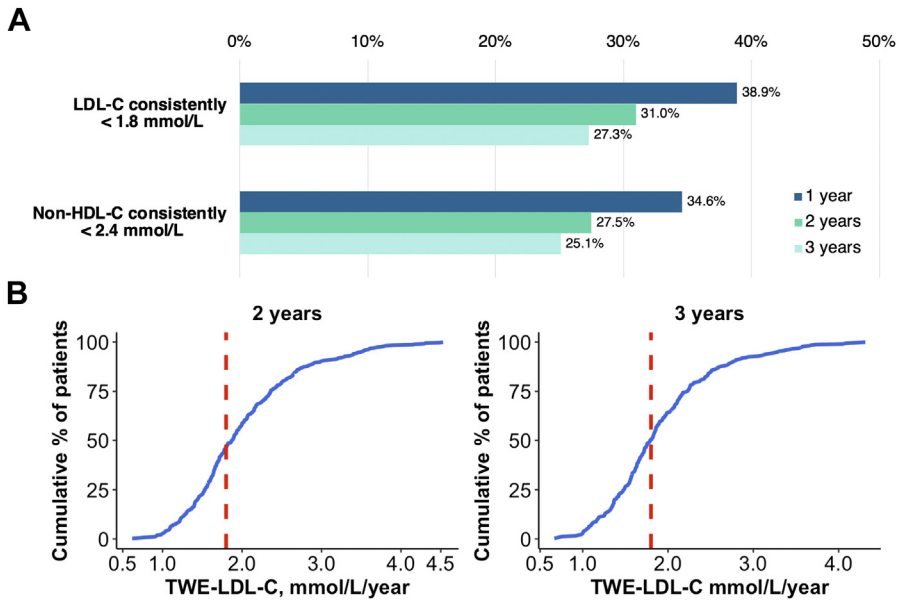
CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol.

findings suggest that the use of TWE-LDL-C as a metric of lipid control is feasible in real-life patient care, can account for these fluctuations, and provides meaningful information for assessing the success of LLT and estimation of short- and long-term benefits.

ROLE OF MEDICATION ADHERENCE IN LIPID CONTROL. The availability of pharmacy dispensation records together with continuous lipid measurements allowed us to explore the role of treatment adherence and potential approaches to treatment optimization. We observed high rates of treatment discontinuation and nonadherence in this contemporary population of patients with premature CAD, in agreement with previous studies.[23-25] After presentation, all patients in the study were prescribed LLT. However, more than 15% of patients either never filled their prescription (primary nonadherence) or were poorly adherent to treatment. By the end of the third year

FIGURE 2 Lipid Values Consistently At Target and Time-Weighted Average LDL-C in 3 Years After Presentation With Premature Coronary Artery Disease



Lipid values consistently at target (A) and time-weighted average LDL-C (B). Proportion of patients with all LDL-C and non-HDL-C values at target decreased from 38.9% and 34.6%, respectively, over the first year after presentation to 27.3% and 25.1%, respectively, over the first 3 years. Over the period of first 2 and 3 years after presentation, approximately half of the patients (46.6% and 50.3%, respectively) had TWE-LDL-C <1.8%. LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; TWE-LDL-C = time-weighted average exposure to low-density lipoprotein cholesterol.

TABLE 2 Attainment of Treatment Targets During First 1, 2, and 3 Years After Presentation With Premature Coronary Artery Disease, Overall and by Adherence to Lipid-Lowering Therapy

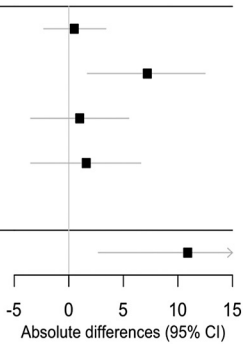
		Adherence Over the Period			
	All Patients	Optimal	Suboptimal	Low	*P* Value
Year 1					
LDL-C <1.8 mmol/L at least once	290 (73.2%)	209 (77.4%)	42 (71.2%)	26 (61.9%)	0.08
LDL reduction >50% from baseline to the lowest value	224 (75.4%)	161 (78.5%)	33 (71.7%)	17 (65.4%)	0.25
LDL-C consistently <1.8 mmol/L	154 (38.9%)	109 (40.4%)	25 (43.1%)	5 (19.2%)	0.09
Year 1 TWE LDL-C <1.8 mmol/L	138 (32.4%)	103 (35.5%)	17 (24.6%)	7 (26.9%)	0.178
Non-HDL-C <2.4 mmol/l at least once	256 (66.1%)	188 (71.2%)	32 (55.2%)	25 (61.0%)	0.04
Non-HDL consistently <2.4 mmol/L	134 (34.6%)	100 (37.9%)	17 (29.8%)	4 (15.4%)	0.049
Years 1-2					
LDL-C consistently <1.8 mmol/L	114 (31.0%)	87 (36.0%)	21 (25.6%)	6 (13.6%)	0.006
Years 1-2 TWE LDL-C <1.8 mmol/L	174 (46.6%)	130 (53.9%)	32 (36.4%)	12 (27.3%)	<0.001
Non-HDL consistently <2.4 mmol/L	96 (27.5%)	68 (30.0%)	21 (26.3%)	7 (16.7%)	0.2
Years 1-3					
LDL-C consistently <1.8 mmol/L	110 (27.3%)	75 (32.5%)	30 (22.6%)	5 (12.8%)	0.013
Years 1-3 TWE LDL-C <1.8 mmol/L	161 (50.3%)	102 (56.7%)	53 (46.1%)	6 (24.0%)	0.005
Non-HDL consistently <2.4 mmol/L	98 (25.1%)	67 (30.2%)	24 (18.6%)	7 (17.9%)	0.03

Values are n (%).

LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; TWE-LDL-C = time-weighted average exposure to low-density lipoprotein cholesterol.

FIGURE 3 Rates of Cardiovascular Outcomes by Time-Weighted Exposure to LDL-C

Outcome	TWE-LDL-C < 1.8 mmol/L	TWE-LDL-C ≥ 1.8 mmol/L	Absolute differences (95% CI)
All-cause death	1.1%	1.7%	0.5% (-2.3-3.4)
Myocardial infarction	3.4%	10.6%	7.2% (1.7-12.5)
Revascularization	4.0%	5.0%	1.0% (-3.5-5.5)
UA and angiography	5.1%	6.7%	1.6% (-3.5-6.6)
Composite outcome	13.1%	24.0%	10.9% (2.7-18.8)



Recurrent MACE occurred in 24.0% of patients with TWE-LDL ≥1.8 mmol/L and 13.1% of patients with TWE-LDL-C <1.8 mmol/L ($P = 0.09$). Among the components of the composite MACE endpoint, non-fatal MI occurred significantly more frequently in individuals with TWE-LDL ≥1.8 mmol/L (10.6%) than in those with TWE-LDL-C <1.8 mmol/L (3.4%, $P = 0.09$). TWE-LDL-C = time-weighted average exposure to low-density lipoprotein cholesterol; UA = unstable angina.

after presentation, less than one-half of patients continuously received LLT with good adherence. When exploring the effects of nonadherence on goal achievement, we observed that patients with nonoptimal adherence were significantly less successful in continuously keeping LDL-C under the recommended threshold. Conversely, we did not observe increased goal achievement in patients who received higher treatment intensity, as has been reported in previous studies.[16,21,37] This may be explained by the high prevalence of inherited dyslipidemias in our study population, which are more common among patients with premature CAD and are associated with a higher risk of cardiovascular outcomes.[26,27] We observed that higher baseline LDL-C was associated with more intensive treatments, but despite the large absolute reduction in LDL-C achieved in many patients, it was not sufficient to keep LDL-C in the recommended goal range.

PRACTICAL IMPLICATIONS. The practical implications of our findings are that while a quarter of patients with premature CAD in the study never achieved their recommended lipid goals and would benefit from access to more potent LDL-C-lowering drugs, for many patients, the primary challenge was treatment nonadherence which was more pronounced when assessed for LLT than other medication classes, indicating a possible role of side effects and intolerance. Such patients could potentially benefit from interventions aimed to improve adherence and treatment options with a more convenient administration regimen. One promising strategy is the earlier use of a combination of therapies at lower doses. This approach was evaluated in the RACING study which demonstrated that the combination of moderate-intensity statin with ezetimibe led to lower rates of drug discontinuation and medication intolerance than high-intensity statin monotherapy.[38]

STUDY LIMITATIONS. Our study has several important limitations. The inclusion criteria are based on angiographically confirmed disease with 50% stenosis, which may limit the generalizability to patients who are managed noninvasively. Patients with atypical symptoms, residents of remote areas, and young females, who may be more likely to have ischemia with nonobstructive coronary arteries, may be underrepresented in the study.

The number of lipid measurements varied between patients, which could affect the precision of longitudinal assessment of target achievement. A small sample size likely limited some statistical testing results. Recurrent unstable angina requiring cardiac catheterization was included in the components of the composite MACE endpoint in multivariable analysis. Finally, treatment adherence was assessed based on pharmacy dispensation records and may be overestimated.

CONCLUSIONS

Among a cohort of contemporary patients with premature CAD, most had lipid levels on target at a

single time point, but less than one-third consistently stayed in the target range during 3 years after presentation. Better cumulative LDL-C control, but not the lowest achieved LDL-C, was associated with lower risk of MACE. Our data highlight the important role of a longitudinal approach to evaluating the efficacy of LLT in research and clinical practice and suggests that TWE-LDL-C could complement the assessment of LDL-C levels at isolated time points to inform decisions on how to optimize lipid management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Most patients with premature CAD can achieve lipid targets when receiving guideline-recommended therapy, but less than one-third consistently stay in the target range. For many patients, the primary challenge contributing for target nonachievement is treatment adherence.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Better cumulative LDL-C control, but not the lowest achieved LDL-C, is associated with lower risk of MACE.

COMPETENCY IN PATIENT CARE: Measurement of longitudinal exposure to LDL-C complements assessment of LDL-C levels at isolated time points to inform decisions on how to optimize lipid management.

TRANSLATIONAL OUTLOOK: Adherence to medication declined over time in patients with premature CAD reflecting challenges of continued lifestyle modification and LLT that may be even more prominent in a primary prevention setting. Studies evaluating the impact of alternative approaches to treatment such as usage of a combination of therapies at lower doses, medications with convenient administration regimen, or longer duration of action on longitudinal lipid control should be conducted.

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KEY WORDS cardiovascular outcomes, longitudinal lipid control, premature coronary artery disease, time-weighted average exposure to LDL-C

APPENDIX For supplemental methods, results, tables, and figures, please see the online version of this paper.