Cardiovascular Topics

Secondary prevention and management of dyslipidaemia in patients with coronary artery disease on statin therapy in a tertiary academic centre in Johannesburg

Patience Ntila, Dineo Mpanya, Nqoba Tsabedze

Abstract

Optimal low-density lipoprotein cholesterol (LDL-C) control in patients with established atherosclerotic cardiovascular disease (ASCVD) is defined as LDL-C levels less than 1.4 mmol/L and a reduction of ≥ 50% in baseline LDL-C levels. This study aims to assess LDL-C control in patients with ASCVD on statin treatment in a tertiary academic hospital. We conducted a cross-sectional study on patients with ASCVD on statin therapy and compared LDL-C levels at the time of presentation with coronary syndromes with the most recent LDL-C obtained during follow-up visits. There were 458 patients with coronary syndromes. After a median duration of 17 months (interquartile range [IQR]: 7–31), 93 (20.3%) patients had optimal LDL-C control. A history of previous coronary artery disease or stroke (odds ratio [OR]: 1.73; 95% confidence interval [CI]: 1.05–2.85; p = 0.031) increased the risk of poor LDL-C control. Only 20.3% of patients with ASCVD on statins achieved the guideline-recommended LDL-C target.

Keywords:: low-density lipoproteins, cholesterol, dyslipidaemia, coronary artery disease, Africa

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Introduction

Globally, elevated levels of low-density lipoprotein cholesterol (LDL-C) are estimated to cause 86.1% of all deaths and disability-adjusted life years (DALYs) due to ischemic heart disease (IHD) and 13.9% due to strokes, accounting for 4.4 million deaths in 2019.[1] In South Africa, dyslipidaemia is estimated to affect 67.3% of the adult population above 45 and 76.7% of the population receiving care for diabetes mellitus and hypertension.[2,3] Furthermore, dyslipidaemia is attributed to 59% of the IHD and 29% of the ischemic stroke burden in the adult population.[4] Sub-Saharan African countries face a growing burden of cardiovascular disease (CVD), with CVD prevention and treatment often overlooked, where the primary focus has been placed on reducing the burden of infectious diseases.[5]

A large body of evidence confirms that a critical precursor in atherosclerosis is the accumulation of LDL particles and other cholesterol-rich apo B-lipoproteins in the media of the arterial walls following previous vascular endothelial injury.[6] For every 1.0 mmol decrease in LDL-C, the incidence of major coronary events, coronary revascularisation, and ischaemic strokes is reduced by approximately 22%.[7] Outcomes from various clinical trials have shown a significant decrease in cardiovascular events proportional to the degree of LDL lowering without an increase in side effects.[8-10] This data prompted the revision of LDL-C targets in 2019 to lower levels than recommended in the 2016 guidelines.[11] Lowering the LDL-C target to even < 1 mmol may be contemplated for patients with ASCVD who experience a recurrence of a vascular event within two years while on maximally tolerated statin-based therapy.[11] Numerous patients on statin monotherapy fail to achieve these LDL-C targets and remain susceptible to future cardiovascular events.[12,13] Adding ezetimibe or proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors to high-intensity statin therapy significantly reduces LDL-C levels.[14,15] Contemporary studies and the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) dyslipidaemia guidelines support the early use of combination therapy.[11,16]

The ESC/EAS and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend a stepwise approach in LDL-C treatment intensification, with statins as the first line lipid-lowering therapy (LLT) and ezetimibe as the second line for patients who are either intolerant to statins or unable to attain recommended LDL-C targets on maximally tolerated doses. Adding PCSK9 inhibitors as a third-line agent is recommended in patients not attaining their LDL-C goals on second-line treatment, or where any second-line treatments are contraindicated.[11,17] High-intensity statins provide at least a 50% decrease in baseline LDL-C levels, ezetimibe 20–27%, while PCSK9 inhibitors provide at least 60%

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reduction either as monotherapy, or a further 46–73% reduction in combination with a maximally tolerated statin or other LLT such as ezetimibe.[8,15,18,19,20,21] Combining statins with ezetimibe further reduces LDL-C levels by 24%.[22]

Data from low- and middle-income countries (LMICs) indicate suboptimal treatment of dyslipidaemia in patients with coronary artery disease (CAD).[23] Several observational studies in South Africa have examined the treatment of dyslipidaemia across public and private healthcare patients with various cardiovascular risk profiles. However, none specifically examined LDL-C targets in the very-high cardiovascular-risk population in a tertiary state-owned hospital.[24-28] Therefore, this study aimed to ascertain the achievement of LDL-C targets in patients with ASCVD on statins treated in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Materials and methods

Study design and sampling

We conducted a cross-sectional single-centre retrospective study on consecutive patients with angiographically proven CAD treated at the CMJAH between 3 April 2017 and 31 December 2019. The CMJAH is a state-owned tertiary academic institution affiliated with the University of the Witwatersrand. The Division of Cardiology within the CMJAH is equipped with an outpatient department with dedicated cardiac speciality clinics, general cardiology wards, a cardiac care unit, as well as electrophysiology and cardiac catheterisation laboratories. The availability of an angiogram report confirming atherosclerotic CAD was the first entry criterion. Patients with angiographically proven CAD on oral statin therapy for at least six weeks, with baseline and follow-up lipograms available, were enrolled in the study. Patients with unspecified coronary syndromes and those who were not on lipid-lowering therapy were excluded from the analysis (Figure 1).

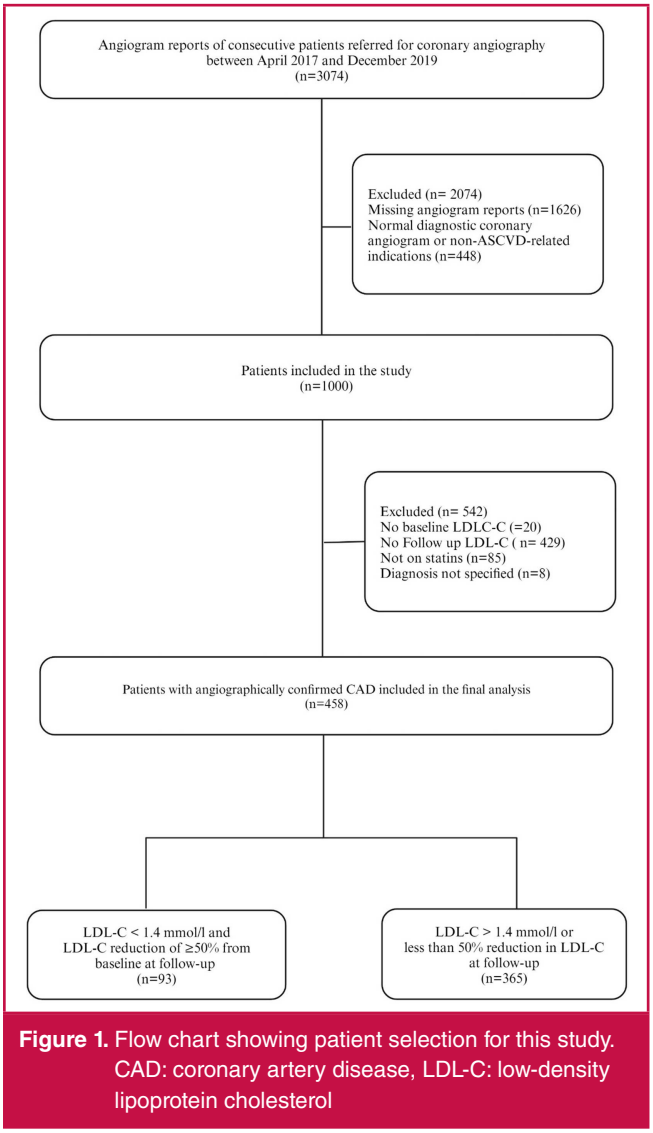

Figure 1. Flow chart showing patient selection for this study. CAD: coronary artery disease, LDL-C: low-density lipoprotein cholesterol

Data collection

We reviewed inpatient and outpatient medical records and patient registers from the cardiac catheterisation laboratory, including archived hard copies and electronic coronary angiogram reports. Variables such as age, gender, medical history, type of ASCVD on presentation, vital signs, electrocardiogram (ECG) and echocardiography findings were captured on the Research Electronic Data Capture (Redcap) database. Demographic information was verified using the hospital Medicom register system. In addition, the National Health Laboratory website was used to obtain laboratory test results, such as renal function tests, lipogram and glycated haemoglobin (HbA1c) levels.

Lipid control

We defined LDL-C targets according to the ESC/EAS 2019 guidelines as LDL-C < 1.4 mmol/L and a reduction of 50% or more in LDL-C from baseline for very high cardiovascular risk.[11] The study cohort was classified as very high cardiovascular risk according to the ESC/EAS 2019 guidelines, since they had established ASCVD. Hypertension and diabetes mellitus were defined according to the World Health Organisation definition. Patients with a systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg or a documented medical history of hypertension were classified as hypertensive, and those on diabetic treatment or with an HbA1c level above 6.5%, were diagnosed as diabetic.[29-31] Dyslipidaemia was defined according to the Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), as a total cholesterol of > 5.2 mmol/L, and/or high-density lipoprotein (HDL) < total cholesterol (TC) 1.0 mmol/L for males, 1.2 mmol/L for females, triglycerides > 1.8 mmol/L and LDL-C ≥ 2.6 mmol/L[32], or patients on lipid-lowering medication. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Statin potency was categorised according to the ACC/AHA cholesterol guidelines of 2018 into high, moderate, or low-intensity statin therapy.[33] Simvastatin 10 mg was the only low-intensity statin therapy used in this cohort, and atorvastatin 10–20 mg daily or simvastatin 20–40 mg daily was used as moderate-intensity statin therapy. Atorvastatin 40–80 mg daily was the only high-intensity statin therapy available. Ezetimibe, at the time of the study, was only

attainable by referral to the lipid clinic at the endocrinology department. A family history of ASCVD was defined as a history of ASCVD in a first-degree relative under the age of 55 and 65 in males and females, respectively.[34] The study was conducted after receiving ethical approval from the University of the Witwatersrand Human Research Ethics Committee (M191183). The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki. Patient consent was waived as the study was a retrospective review of medical records. The Gauteng Department of Health also approved the research proposal and granted access to the medical records.

Data analysis

All statistical analyses were conducted using Stata version 18.5 (College Station, Texas: Stata Corp LLC). Categorical data were summarised as frequencies and percentages and were compared using the Pearson's Chi-square test. Histograms and normality tests, such as the skewness and the Shapiro-Wilk tests, were used to assess the distribution of continuous variables. Normally distributed variables were summarised using means and standard deviation, and when the distribution was non-normal, the medians and interquartile range (IQR) were used. To compare normally distributed data, parametric tests such as the paired Student t-test were used for continuous data, and the Wilcoxon rank sum test was used for non-parametric continuous data. Univariable and multivariable logistic regression analyses were conducted to identify predictors of poor lipid control among patients with established ASCVD. All variables with a p-value less than 0.1 after conducting the Pearson's Chi-square test, Student t-test, or Wilcoxon rank sum test were selected for further exploration in the univariable logistic regression model. Variables with a p-value less than 0.05 on univariable analysis were subsequently included in the multivariable logistic regression model. Confidence intervals were set at 95%, and a p-value less than 0.05 was considered a threshold for statistical significance for all statistical tests.

Result

Baseline demographic characteristics and comorbidities

The final study population comprised 458 patients, of whom 384 (83.8%) were hospitalised with acute coronary syndromes. The mean age was 60 ± 11.2 years, and males comprised 328 (71.6%) of all patients. Among the 27 patients with LDL-C levels above 4.9 mmol/L, 59.3% were Caucasian. A history of smoking was documented in the records of 299 (65.3%) patients. There were 325 (70.9%) patients with hypertension, 290 (63.3%) with dyslipidaemia, and 172 (37.5%) with diabetes mellitus. The rest of the baseline characteristics are presented in Table 1.

Types of statins used and achievement of LDL-C levels

Baseline LDL-C levels, obtained during presentation with coronary syndromes at follow-up during an outpatient visit, are shown in Figure 2. There were 198 (43.2%) patients with a baseline LDL-C between 3.0 and 4.89 mmol/l, and the mean

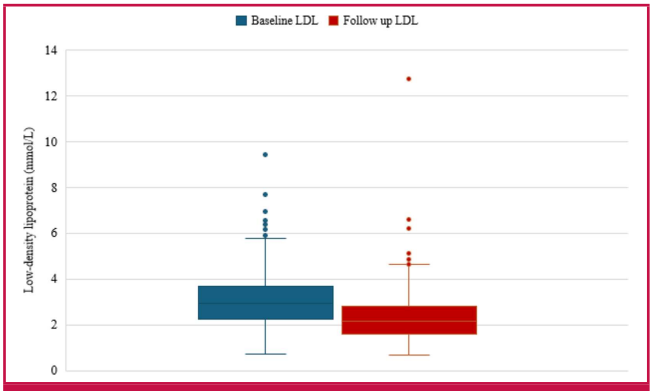

Figure 2. Box-and-whisker plot showing LDL-C levels at the time of the coronary event and during follow-up at an outpatient visit after a median duration of 17 months (IQR: 7–31). LDL: low-density lipoprotein, IQR: interquartile range

LDL-C in the study population was 3.06 ± 1.2 mmol/L. Patients on high-intensity statin therapy comprised 329 (71.8%), while 132 (28.8%) were on moderate-intensity statin therapy. The mean dose of simvastatin used was 37.5 ± 6.9 mg daily and 73.7 ± 15.3 mg daily for atorvastatin. One patient was on combination therapy with a high-intensity statin and a selective cholesterol absorption inhibitor, ezetimibe.

After a median duration of 17 months (IQR: 7–31), 93 (20.3%) patients achieved LDL-C targets (Figure 3). Of these patients who attained LDL-C targets, 76 (16.6%) were on high-intensity statin therapy and 17 (3.7%) on moderate-intensity statin therapy. Patients who attained the LDL-C target had a higher baseline mean TC of 5.6 ± 1.4 mmol, compared to those who did not attain LDL-C targets, with mean TC levels of 4.5 ± 1.2 mmol ($p < 0.001$). Furthermore, patients who did not achieve follow-up LDL-C targets had either an insufficient reduction in LDL-C levels to target, as observed in 232 (63.6%) patients, or no change in LDL-C levels, as observed in 12 (3.3%) patients. An increase from baseline in LDL-C levels was observed among 121 (33.1%) patients. Patients attaining LDL-C targets had a higher mean diastolic blood pressure (84 ± 18.1, 95% CI: 80–88 mmHg) than patients without a significant reduction in LDL-C levels (79 ± 16.2, 95% CI: 77–81 mmHg, $p = 0.016$).

Predictors of failure to achieve LDL-C targets

On univariable logistic regression analysis, a previous history of CAD or cerebrovascular accidents (CVA) (OR: 1.73; 95% CI: 1.05–2.85; $p = 0.031$) and unstable angina (OR: 2.25; 95% CI: 1.08–4.70; $p = 0.030$) were associated with an increased risk of not attaining LDL-C targets (Table 2). On multivariable logistic regression analysis, none of the variables independently predicted failure to attain LDL-C targets.

Discussion

We conducted a cross-sectional retrospective study on consecutive patients with angiographically proven CAD, and compared their serum LDL-C levels (measured at the time

Table 1. Baseline demographic and clinical characteristics of patients with coronary syndromes stratified according to target LDL-C levels obtained during the follow-up outpatient visit

		Optimal LDL-C control		
	All patients (n = 458)	*Yes n = 93 (20.3%)*	*No n = 365 (79.7%)*	*p-value*
Age, years (mean, SD)	60 ± 11.2	59 ± 11.0	60 ± 11.2	0.4339
Male (%)	328 (71.62)	65 (69.89)	263 (72.05)	0.680
Ethnicity (%)				
Caucasian	199 (43.4)	38 (40.9)	161 (44.1)	0.334
Asian/Indian	128 (27.9)	32 (34.4)	96 (26.3)	
Black	85 (18.6)	18 (19.3)	67 (18.4)	
Mixed ancestry	45 (9.8)	5 (5.4)	40 (11.0)	
Cardiovascular risk factors (%)				
Hypertension	325 (71.0)	61 (65.6)	264 (72.3)	0.201
Previous stroke or CAD	172 (37.7)	26 (28.0)	146 (40.2)	0.029
Diabetes mellitus	172 (37.5)	34 (36.6)	138 (37.8)	0.824
Dyslipidaemia	290 (63.3)	62 (66.7)	228 (62.5)	0.453
Smoker	299 (65.3)	58 (62.4)	241 (66.0)	0.508
Peripheral vascular disease	16 (3.5)	4 (4.3)	12 (3.3)	0.635
Family history of CAD	181 (39.5)	29 (31.2)	152 (41.6)	0.065
Chronic kidney disease	66 (14.4)	8 (8.6)	58 (15.9)	0.074
HIV	15 (3.3)	3 (3.2)	12 (3.3)	0.976
Vital signs				
Heart rate (b/min)	74 (66–86)	74 (66–90)	74 (66–86)	0.9307
Systolic BP (mmHg)	124(112–141)	124 (111–150)	124 (112–140)	0.5086
Diastolic BP (mmHg), SD	80 ± 16.7	84 ± 18.1	79 ± 16.2	0.0106
Laboratory indices				
Total cholesterol (mmol/L)	4.7 ± 1.3	5.6 ± 1.4	4.5 ± 1.2	0.001
HDL (mmol/L)	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	0.0782
TG (mmol/L)	1.7 ± 1.1	1.7 ± 1.5	1.7 ± 1.2	0.9903
Type of coronary syndrome on presentation (%)				
STEMI	186 (40.6)	39 (41.9)	147 (40.3)	0.771
NSTEMI	118 (25.7)	33 (35.5)	85 (23.3)	0.016
Unstable angina	80 (17.5)	9 (9.7)	71 (19.4)	0.027
Stable angina	74 (16.2)	12 (12.9)	62 (17.0)	0.340
Medication				
Anti-hypertensives	438 (95.6)	91 (97.8)	347 (95.1)	0.241
Oral hypoglycaemic agents	143 (31.2)	27 (29.0)	116 (31.8)	0.610
Atorvastatin 10–20 mg	6 (1.3)	0 (0.0)	6 (1.6)	
Atorvastatin 40–80 mg	329 (71.8)	76 (81.7)	253 (69.3)	0.006
Simvastatin 20–40 mg	123 (26.9)	17 (18.3)	106 (29.0)	0.015

SD: standard deviation, CAD: coronary artery disease, HIV: Human immunodeficiency virus, BP: blood pressure, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, TG: triglycerides, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction
Categorical variables are expressed as frequencies and percentages. Continuous variables with a normal distribution are expressed as the mean and standard deviation, and those with a non-normal distribution are expressed as the median and interquartile range.

of presentation with the coronary syndrome) with the most recent LDL-C levels measured during an outpatient visit. The key finding was the failure to achieve LDL-C targets in 79.7% of the study population. Furthermore, only 71.8% of patients were on a high-potency statin. On univariate logistic regression analysis, patients presenting with NSTEMI were less likely to have suboptimal LDL-C target levels, while unstable angina and a history of previous CAD or CVA increased the risk of failure to achieve the ideal LDL-C target. None of these clinical parameters independently predicted failure to attain an optimal LDL-C target. We hypothesise that the association between unstable angina and failure to achieve LDL-C targets on univariable regression analysis could be accounted for by the reluctance of treating physicians to initiate high-potency statins in ACS presentations other than STEMI and NSTEMI. Notably, most of the patients with STEMI did not attain target LDL-C levels. Current evidence-based guidelines advise initiating high-intensity statins in all patients with ACS, irrespective of ACS presentation or baseline LDL-C levels. These recommendations are supported by evidence from studies showing the benefit of early high-intensity statin prescription.[35-37]

Although patients who attained guideline-recommended LDL-C targets started with higher baseline total cholesterol levels, 81.7% were on a high-intensity statin compared to 69.3% of those who failed to attain the ideal LDL-C goal (p = 0.006). Thirty per cent (30.6%) of patients who did not attain LDL-C targets were inappropriately on moderate-intensity statins. A previous history of CAD or CVA was associated with failure to achieve LDL-C targets. We hypothesise that these patients were already on statin therapy at the time of presentation with coronary syndromes and already had uncontrolled LDL-C levels when they presented with a second cardiovascular event. As a

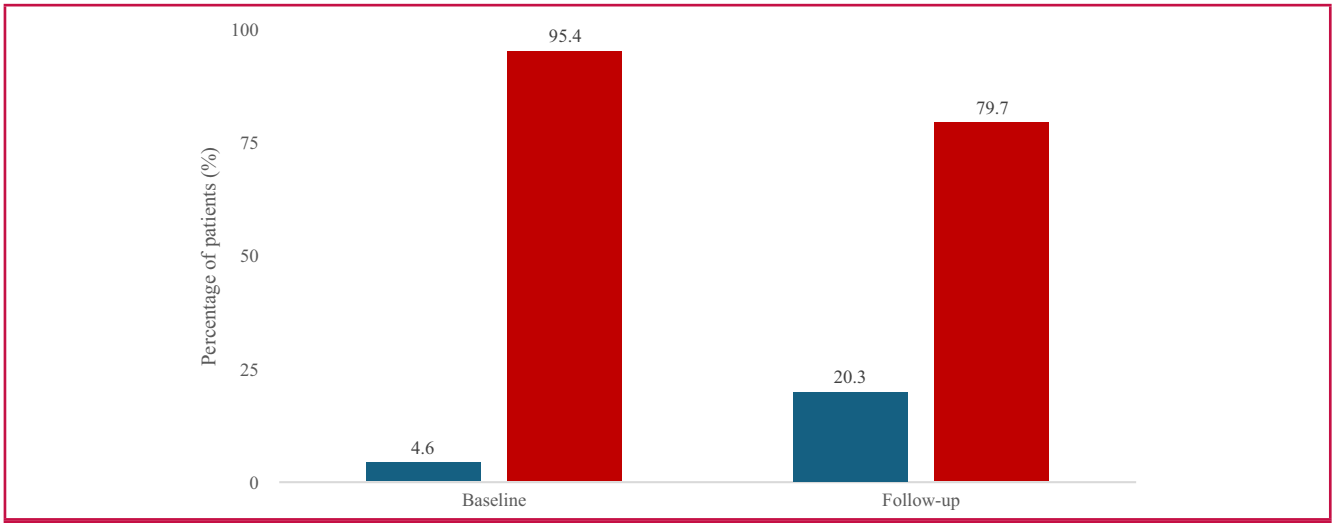

Figure 3. Patients with target LDL-C levels at presentation with coronary syndromes (at baseline) and follow-up after a median duration of 17 months (IQR: 7–31). At the time of presentation with coronary syndromes, 4.6% of patients had LDL-C levels less than 1.4 mmol/L (blue bar). At the follow-up visit, 20.3% of all patients achieved target LDL-C levels (LDL-C less than 1.4 mmol/L) and a 50% or more reduction in the LDL-C level at subsequent visits. The rest of the patients (79.7%) failed to achieve LDL-C targets, despite being on treatment (red bar).

result, there was a modest or no increase in LDL-C levels at follow-up.

We also found that patients with coronary syndromes and higher diastolic blood pressure were more likely to attain the recommended LDL-C targets, probably due to frequent follow-ups with regular up-titration of medications, as these patients might have been deemed very high risk by clinicians due to poor blood pressure control. Across all racial groups, most patients failed to achieve LDL-C targets, with the majority being Caucasian. In our study, more than half of all Caucasians had baseline LDL-C levels above 4.9 mmol/L. Although a history of familial hypercholesterolemia (FH) was suspected in these patients, we could not confirm this diagnosis. Familial hypercholesterolemia is more prevalent in Caucasians and, to a lesser extent, in the Asian population. Patients with FH usually have higher baseline LDL-C and find it harder to achieve LDL-C targets on statin therapy alone.[38,39]

Table 2. Univariable and multivariable logistic regression analysis for predictors associated with failure to attain LDL-C targets during the follow-up visit

	Univariable analysis		*Multivariable analysis*	
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
Family history of CAD	1.57 (0.97–2.56)	0.067		
Previous CAD/CVA	1.73 (1.05–2.85)	0.031	1.67 (1.00–2.78)*	0.048
Chronic kidney disease	2.00 (0.92–4.37)	0.079		
Unstable angina	2.25 (1.08–4.70)	0.030	1.71 (0.79–3.69)	0.169
NSTEMI	0.55 (0.34–0.90)	0.017	0.61 (0.36–1.01)	0.055

*Results are not considered to be statistically significant since the confidence interval includes one.
OR: odds ratio, CI: confidence interval, CAD: coronary artery disease, CVA: cerebrovascular accident, NSTEMI: non-ST-segment elevation myocardial infarction

In middle-income countries such as Thailand, higher rates of utilisation of high-intensity statins were observed. Findings from a tertiary hospital database in Thailand reported that high-intensity statins were taken by 56.3% of patients with ACS. Also, only 43.3% of patients had optimal LDL-C targets on follow-up. Although the high-intensity statin prescription rate was lower than in our study, most of their patients attained LDL-C targets. Multiple environmental, genetic, and behavioural factors may explain this finding. In South Africa, Blom *et al.* reported optimal LDL-C control in only 41.4% of their study population, predominantly private-funded patients.[28] Their study population's demographic profile and underlying comorbidities were comparable to ours. Of note, the prescription rate of combination therapy with ezetimibe was reported to be as low as 13.8%.

An interplay between iatrogenic, genetic, medication, and other patient-related factors could have contributed towards poor LDL-C control in our study population. Some of the physician-related contributory factors are failure to initiate high-intensity statin on all patients irrespective of ACS presentation or lipid levels, the inertia to actively titrate lipid-lowering therapy at follow-up visits, lack of knowledge of guidelines regarding LDL-C targets, CVD risk estimation, and reluctance to use and inaccessibility of non-statin combination therapies.[40,41] Patient and socioeconomic or drug-related factors, such as non-adherence, statin intolerance, and economic and geographical hindrances to access health care, are also some of the contributing factors.[42,43,44] Moreover, variability in statin metabolism has been reported amongst specific populations.[45,46]

Despite various studies showing the incremental lowering of LDL-C with combination therapy using statins and PCSK9 inhibitors or ezetimibe, access and cost remain significant limitations to their use in LMIC, particularly in state-funded hospitals.[8,14,15] Patients attending state-owned facilities only have

access to low and moderate-intensity statins. To access high-intensity statin or ezetimibe, patients would require referral to a tertiary-level or quaternary hospital with a specialist-driven lipid clinic.

There is a need for improved access to contemporary non-statin lipid-lowering therapy, such as ezetimibe and PCSK9 inhibitors, considering that most patients fail to achieve guideline-recommended LDL-C targets despite the high utilisation of high-intensity statins. Furthermore, patients with CAD still have a residual risk of major adverse cardiovascular events, despite achieving optimal LDL-C targets. This is due to endothelial dysfunction caused by the chronic inflammation in the endothelial lining of the coronary arteries.[47]

Limitations

Our study had several limitations. The sample size was relatively small, and the patients studied were from a single tertiary centre, suggesting that our findings may not be generalisable to patients treated in primary or secondary-level hospitals. When the study was conducted, there was a transition from the 2016 to the 2019 EAS/ESC guidelines. As such, LDL-C control in patients hospitalised between 2017 and 2018 was assessed based on recommendations listed in the 2019 EAS/ESC guidelines on the management of dyslipidaemia. We could not exclude non-compliance as a factor. We could not exclude non-compliance as a factor; this information was poorly documented in the patient records. Also, in patients with a prior history of CVA or myocardial infarction, it was not possible to determine whether these patients were already on statin therapy or not at the time of admission for an acute coronary syndrome. Despite these limitations, our study showed that optimal LDL-C control is challenging, even in patients managed in specialised outpatient cardiac clinics.

Conclusion

Only 20.3% of patients with coronary syndromes had optimal LDL-C control during the follow-up visit. More research is essential to ascertain the efficacy and cost-effectiveness of combination lipid-lowering therapy in low-and middle-income countries.

Author's contributions

PN was involved in the study design, data collection and visualisation, and manuscript writing. NT and DM predefined the research question, supervised the study, and edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of interest

NT is a cardiologist and has received consultation fees from Acino Health Care Group, AstraZeneca, Boston Scientific, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Sanofi, Phillips, Servier, Takeda, and Merck. He has also received educational and travel grants from Medtronic, Biotronik, Boston Scientific and Vertice Health Care Group. No other authors have any relevant financial or professional disclosures.

Conflict of interest statement

No potential conflict of interest was reported by the author(s).

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