Low-density lipoprotein cholesterol goal attainment and mortality in ischaemic heart disease: a two-year observational study

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Abstract

Introduction: Achieving low-density lipoprotein cholesterol (LDL-C) levels is key to preventing atherosclerotic cardiovascular events. However, many high-risk cardiovascular patients still experience poor LDL-C goal attainment and receive suboptimal lipid-lowering therapy (LLT) prescriptions. Herein, we evaluated LLT prescription patterns, LDL-C goal attainment and cardiovascular mortality among this population group in Singapore.

Methods: This prospective observational cohort study included 555 patients with ischaemic heart disease (IHD) admitted to the hospital in 2020. The LLT prescriptions, corresponding LDL-C levels and cardiovascular outcomes were assessed over a 24-month period.

Results: Most participants were male (82.3%), with 48.5% identified as Chinese. High-intensity statin prescriptions increased from 45.4% at hospital admission to 87.1% at discharge and remained stable at approximately 80% at 6, 12, and 24 months post-discharge. Combination LLT prescriptions increased from 12.3% at discharge to 33.8% by 24 months. Ezetimibe was the most commonly prescribed second-line LLT (40.8%), followed by inclisiran (1.09%) and anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibody therapies (0.87%). Over 24 months, LDL-C goal attainment rates were 22.1% for LDL-C < 1.4 mmol/L and 47.2% for LDL-C < 1.8 mmol/L. Multivariable Cox proportional hazards regression indicated that achieving LDL-C < 1.8 mmol/L goal was associated with a reduction in all-cause mortality at 24 months (hazard ratio 0.53, 95% confidence interval 0.30–0.94, $P = 0.030$).

Conclusion: Treatment gaps in lipid management persist in 80% of the study population, indicating that statin monotherapy alone is insufficient to achieve LDL-C goals. Greater efforts to improve LDL-C goal attainment rates in high-risk cardiovascular patients are imperative.

Keywords: Cardiovascular disease, LDL-C, lipid-lowering therapy, mortality

INTRODUCTION

Statins pharmacotherapy is the most prescribed lipid-lowering therapy (LLT) worldwide due to its importance in the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events.[1,2] In addition to statins, clinically accessible LLTs in Singapore include ezetimibe, bile acid sequestrants, and agents that inhibit the proprotein convertase subtilisin/kexin type 9 (PCSK9) pathway. These agents include monoclonal antibodies such as evolocumab and alirocumab, as well as inclisiran, a small interfering ribonucleic acid.[3–6] With the availability of safe and effective low-density lipoprotein cholesterol (LDL-C) lowering therapies and strong scientific evidence that lowering LDL-C reduces ASCVD events, multiple international cardiovascular guidelines have recommended more aggressive LDL-C lowering, adhering to

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SUMMARY BOX

What is known?

Lowering low-density lipoprotein cholesterol (LDL-C) is a central objective in the management of ischaemic heart disease.

What is new?

Our study reported that approximately 80% and 60% of high-risk cardiovascular patients did not achieve LDL-C goals of < 1.4 mmol/L and < 1.8 mmol/L, respectively. Statin monotherapy often proved insufficient to lower LDL-C levels.

What is the impact?

Our findings align with large observational studies, underscoring a significant gap between clinical guidelines and practice. This highlights a global need to improve LDL-C goal attainment rates. Early initiation of lipid-lowering combination therapies may be beneficial.

the general motto, 'the lower, the better', for all patients at very high cardiovascular risk.[1,2]

Despite advancements in the medical field, suboptimal LDL-C goal attainment rates continue to be reported in numerous recent large studies. The European-based DA VINCI study in 2019 found that only 38% of high-risk patients with ASCVD were prescribed high-intensity statins, and only 22% of these patients achieved their target LDL-C goals of < 1.4 mmol/L.[7] Similarly, the SANTORINI study of European patients conducted in 2020–2021 reported that only 20% of high-risk and very-high-risk patients achieved their recommended LDL-C goals.[8] In the United States, a retrospective study of 25,339 patients found that only 27.4% of patients had achieved an LDL-C target of < 1.8 mmol/L.[9] In Asia, the DYSIS II study (across nine countries in the Asia-Pacific region) found that only 31% of patients with coronary heart disease and 23% of patients admitted with acute coronary disease achieved an LDL-C level of < 1.8 mmol/L.[10]

These studies show that large gaps clearly exist between clinical guidelines and clinical practice, leading to suboptimal LDL-C goal attainment rates in patients at high or very high risk for cardiovascular events in real-world settings.[8–10] In this study, we aimed to assess contemporary prescription patterns of LLT and LDL-C goal attainments in patients with ischaemic heart disease (IHD) admitted to the hospital. We also assessed their clinical outcomes, including all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (MACE) within 24 months.

METHODS

This is a single-centre, prospective cohort study of patients with IHD admitted to cardiology wards. All patients in this study were diagnosed with IHD and admitted to the cardiology unit for cardiac-related complications or symptoms, placing them at very high risk for further cardiovascular events. In our study, IHD was defined as a clinical diagnosis of IHD, coronary artery disease or ischaemic cardiomyopathy, or a history of requiring coronary stent intervention or coronary artery bypass graft surgery, or a history of myocardial infarction, as indicated in the case notes or electronic medical records. The patients described in this study were recruited during hospitalisation between 1 June 2020 and 31 December 2020 at Changi General Hospital, a 1000-bed tertiary hospital in eastern Singapore.[11] Recruited participants were consenting patients aged ≥ 21 years. Medication prescriptions and blood results were obtained from electronic medical records at various time points, including upon hospital admission, discharge from hospital, and at the 6 month-, 12 month-, and 24 month-marks after discharge. A window period of 2 months was used at the 6-month time point, and ± 2 months at the 12- and 24-month time points. High-intensity statin was defined as doses of atorvastatin ≥ 40 mg or its equivalent, i.e. rosuvastatin 20–40 mg.[12] For the purposes of the study, only physician-prescribed formulary omega-3 supplements (1 g of omega-3-acid ethyl esters per capsule) were included in data collection. Over-the-counter supplements were excluded from the study because most patients could not verify or quantify the omega-3 content of the fish oil they were taking, and only a minority of patients consumed over-the-counter supplements. Blood concentrations for total cholesterol, high-density lipoprotein cholesterol, direct LDL-C, and triglyceride levels were measured in our hospital laboratory using an enzymatic colorimetry Roche Cobas c702 analyser (Roche Diagnostics International AG, Rotkreuz, Switzerland), with inter-assay CVs < 1.5%. This study was approved by our institution's ethics committee (CIRB No.: 2020/2065).

Patient outcomes included all-cause and cardiovascular-related deaths, as well as all cardiovascular readmissions. Cardiovascular rehospitalisation was defined as hospital admissions due to heart failure stroke, acute myocardial infarction (AMI) or any coronary revascularisation, including elective admissions for percutaneous coronary intervention or coronary artery bypass graft surgery. Cardiovascular mortality was defined as deaths from AMI, IHD, ischaemic stroke, end-stage heart failure, and other cardiovascular-related causes. All-cause mortality included both cardiovascular- and non-cardiovascular-related deaths. A composite MACE index was defined as a combination of all-cause mortality and cardiovascular hospital readmissions, as previously defined. The cause of deaths for patients who passed away outside of the hospital, with no available hospital data on the cause of death, was classified as non-cardiovascular-related deaths in our study, as we did not have access to the cause of death for these patients.

Descriptive statistics of patient demographics and clinical characteristics were reported as numbers and percentages for categorical data, mean ± standard deviation for normally

distributed data, and median and interquartile range for non-normally distributed data. Univariable and multivariable logistic regression were used to identify factors associated with achieving the LDL-C goal of < 1.8 mmol/L at any time during the follow-up period. To examine whether LDL-C goal attainment was associated with a subsequent reduced risk of mortality and other cardiovascular outcomes, multivariable Cox proportional hazards regression was performed, with time to outcome as the dependent variable and LDL-C goal attainment as the independent variable. Attainment of LDL-C goal was defined as achieving the target at any time within 12 months after hospitalisation, to allow sufficient time for LDL-C goal attainment and the occurrence of mortality/MACE. Adjustments were made using variables for baseline LDL-C, age at first visit, sex, race, body mass index (BMI), smoking status, hypertension, diabetes mellitus, chronic kidney disease, and hospital admission for AMI and other MACE events. The proportional hazards assumption of the Cox regression was assessed using a test based on Schoenfeld residuals. The Box–Tidwell test was used to assess evidence of non-linearity between ln (hazard) and continuous explanatory variables. For both tests, a P value < 0.05 indicated a violation of the proportional hazards and linearity assumptions, respectively. Where evidence of non-linearity was found, a restricted cubic spline function with three knots at the 10th, 50th and 90th percentiles was used to model the relationship between the continuous explanatory variables and the outcome. In cases of mild violation of the proportional hazard assumption, Huber–White standard errors were used to estimate the time-averaged hazard ratio (HR). The unadjusted and adjusted HRs and odds ratios (ORs), with corresponding 95% confidence intervals (CIs), were reported. Statistical tests were two-sided, with a significance level of 0.05. All statistical analyses were conducted using Stata version 18 (StataCorp LP, College Station, TX, USA) and 'Med4way' package2.

RESULTS

Patient characteristics

Figure 1 shows the CONSORT diagram of the 555 consenting patients. A total of 83 patients died within the next 24 months, with three of these deaths occurring during the same hospital admission. Table 1 describes the clinical characteristics of all the study participants, stratified by whether they achieved LDL-C < 1.8 and ≥ 1.8 mmol/L within 12 months. The median age of study participants at baseline was 63.8 years, 82.3% were male, and 48.5% were of Chinese ethnicity. The median BMI was 25.1 kg/m^2, with 30.6% of study participants having obesity (BMI ≥ 27.5 kg/m^2). Active smoking was prevalent (28.3%). Only 3.7% of patients consumed alcohol above the national guideline limits. A total of 47.9% of patients had type 2 diabetes mellitus, 79.3% had hypertension, 82.2% had hypercholesterolaemia, and 24.5% had chronic kidney disease. Elevated lipoprotein (a) [Lp (a)] ≥ 120 nmol/L was present in 15.6% of patients, with a median Lp (a) level of 35.2 nmol/L. Half of the study participants (50.3%) were admitted to the hospital for an AMI event.

Statin therapy

Table 2 shows the trend of statin and other LLT prescriptions over 24 months. Approximately 68.6% of patients were already prescribed statins upon hospitalisation. The prescription rate of statin therapy increased significantly to 97.1% (P < 0.001) at discharge and remained similarly high in subsequent months (93.5% at 6 months, 92.7% at 12 months and 97.6% at 24 months). The prescription rate of high-intensity statins

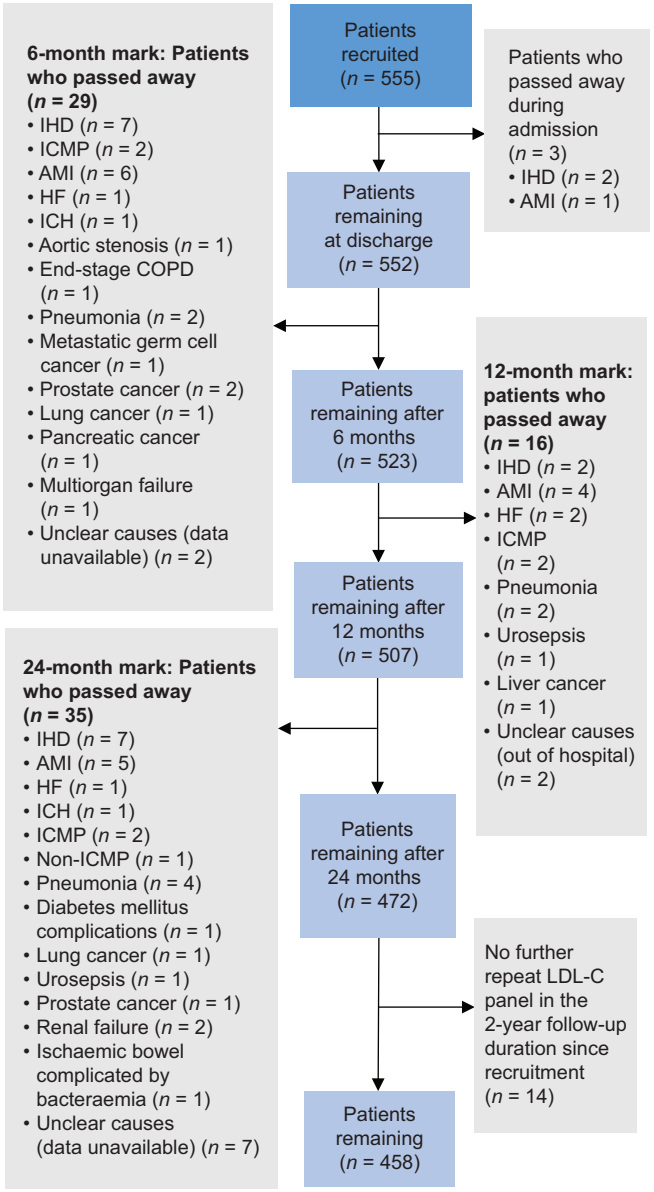

Figure 1: Consort diagram shows the patient recruitment process for the study. All patients had a clinical diagnosis of ischaemic heart disease (IHD) at the time of recruitment. AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, HF: heart failure, ICH: intracranial haemorrhage, ICMP: ischaemic cardiomyopathy, LDL-C: low-density lipoprotein cholesterol

Table 1. Baseline characteristics of study participants, stratified by patients who achieved LDL-C ≥ 1.8 mmol/L or < 1.8 mmol/L by the 12-month period.

Characteristic	*n* (%)/Median [IQR]		
	All patients (*n*=555)	LDL-C ≥ 1.8 mmol/L (*n*=205)	LDL-C < 1.8 mmol/L (*n*=350)
Age at admission (yr)	63.8 [56.4–71]	62.2 [54.4–70.3]	64.4 [58–71.4]
Age group at admission (yr)			
< 50	66 (11.9)	36 (17.6)	30 (8.6)
50–59	133 (24.0)	52 (25.4)	81 (23.1)
60–69	192 (35.6)	63 (30.7)	129 (36.9)
70–79	114 (20.5)	38 (18.5)	76 (21.7)
≥ 80	50 (9.0)	16 (7.8)	34 (9.7)
Male gender	457 (82.3)	162 (79.0)	295 (84.3)
Ethnicity			
Chinese	269 (48.5)	82 (40.0)	187 (53.4)
Malay	179 (32.3)	79 (38.5)	100 (28.6)
Indian	70 (12.6)	29 (14.2)	41 (11.7)
Others	37 (6.7)	15 (7.3)	22 (6.3)
BMI at baseline (kg/m^2)	25.1 [22.4–28.4]	25.4 [22.8–28.3]	24.9 [22.3–28.4]
Chronic condition			
Hypertension	440 (79.3)	158 (77.1)	282 (80.6)
Hypercholesterolemia	456 (82.2)	185 (90.2)	271 (77.4)
Type 2 diabetes mellitus	266 (47.9)	95 (46.3)	171 (48.9)
Congestive heart failure	185 (33.8)	57 (28.2)	128 (37.1)
Stroke	70 (12.7)	19 (9.4)	51 (14.7)
Chronic kidney disease	136 (24.5)	48 (23.4)	88 (25.1)
Ischaemic heart disease	261 (47.0)	106 (51.7)	155 (44.3)
History of AMI	139 (25.1)	46 (22.4)	93 (26.6)
Smoker	157 (28.3)	81 (39.5)	77 (22.0)
Admitted to hospital for AMI	279 (50.3)	117 (57.1)	162 (46.3)
Biomarker at baseline			
LDL-C (mmol/L)	2.41 [1.78–3.46]	3.08 [2.35–4.2]	2.01 [1.51–2.98]
HDL-C (mmol/L)	1.13 [0.94–1.33]	1.13 [0.95–1.31]	1.14 [0.94–1.35]
Triglycerides (mmol/L)	4 [3.25–5.04]	4.59 [3.85–5.81]	3.6 [2.91–4.53]
Lp (a) (nmol/L)	35.2 [16.3–80.3]	50.5 [23.6–101.8]	31.5 [13.5–67.3]
ApoA (g/L)	1.2 [1.05–1.37]	1.18 [1.06–1.36]	1.2 [1.05–1.38]
ApoB (g/L)	0.89 [0.7–1.1]	1.04 [0.87–1.26]	0.81 [0.63–0.98]
CRP (mg/L)	6.04 [1.59–20.3]	7.82 [1.91–25.9]	5.17 [1.42–17.8]
Trop T (ng/L)	95.3 [19.4–899]	155 [23.6–941]	78.4 [19.2–847]
Ejection fraction (%)	40 [30–55]	40 [25–55]	40 [30–55]
< 50	350 (64.2)	136 (67.7)	214 (62.2)
≥ 50	195 (35.8)	65 (32.3)	130 (37.8)

ApoA: apolipoprotein A, ApoB: apolipoprotein B, AMI: acute myocardial infarction, BMI: body mass index, CRP: c-reactive protein, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, LDL-C: low-density lipoprotein cholesterol, Lp (a): lipoprotein (a), Trop T: troponin T

increased from 45.4% at hospital admission to 87.1% at discharge ($P < 0.001$) and remained consistently high at 79.9%, 79.3% and 84.0% at 6, 12 and 24 months, respectively. Among the statins prescribed, atorvastatin 40 mg was the most common prescription at discharge (45%). Of the 15 patients who were not discharged from hospital with statin therapy, six had liver enzyme derangements on blood tests, one had liver cirrhosis, and one had a hepatic abscess. One patient did not receive statins due to a history of rhabdomyolysis related to previous statin use. Statin was discontinued in one patient at follow-up because he was subsequently found to have terminal cancer. The reasons for discontinuation were not explicitly stated for the remaining five patients, and statins were gradually reintroduced into their medical regimen.

Other lipid-lowering therapies

At baseline, the percentage of patients on combination therapy (both high-intensity statin and either ezetimibe or PCSK-9-targeted therapies) was low at 6.49%. The prescription rate of combination therapy (LLT) increased to 12.3% on discharge, 21.0% at 6 months, 27.4% at 12 months and

Table 2. Percentage of patients and their respective lipid-lowering therapy (LLT) prescriptions at different timepoints.

Variable	*n* (%)				
	Hospitalisation (*n*=555)	Discharge (*n*=552)	6 months (*n*=523)	12 months (*n*=507)	24 months (*n*=458)
Statin intensity	381 (68.6)	536 (97.1)*	489 (93.5)*	470 (92.7)*	447 (97.6)*
High	252 (45.4)	481 (87.1)*	418 (79.9)*	402 (79.3)*	385 (84.0)*
Moderate	107 (19.3)	53 (9.60)	70 (13.4)	67 (13.2)	61 (13.3)
Low	22 (3.96)	2 (0.36)	1 (0.19)	1 (0.20)	1 (0.22)
Other LLT	76 (13.7)	106 (19.2)	151 (28.9)	179 (35.3)	204 (44.5)
Ezetimibe	41 (7.39)	77 (13.9)	127 (24.3)	157 (31.0)	187 (40.8)†
Fenofibrate	31 (5.59)	26 (4.71)	22 (4.21)	26 (5.12)	24 (5.24)†
Omega-3	13 (2.34)	16 (2.90)	19 (3.63)	18 (3.55)	22 (4.80)
PCSK9 monoclonal inhibitors[a]	0 (0)	1 (0.18)	2 (0.38)	2 (0.39)	4 (0.87)
Inclisiran	0 (0)	0 (0)	0 (0)	0 (0)	5 (1.09)
Combination therapy[b]	36 (6.49)	68 (12.3)	110 (21.0)	139 (27.4)	155 (33.8)†

[a]Refers to evolocumab, alirocumab and inclisiran. [b]Includes high-intensity statin and ezetimibe/PCSK9 agents. *P<0.001 when comparing against the LLT prescription rate at hospitalisation. †P<0.001 when comparing LLT prescription at point of discharge and at 24 months. PCSK9: proprotein convertase subtilisin/kexin type 9

33.8% at 24 months (P < 0.001). On admission to the hospital, only 13.7% of the patients were prescribed a non-statin LLT, and by the time of hospital discharge, 19.3% were prescribed a non-statin LLT. The prescription rates of other LLTs (mainly from ezetimibe) increased gradually to 29.0% at 6 months, 35.5% at 12 months, and 44.5% at 24 months after discharge from the hospital (P < 0.001). Ezetimibe was the most common second-line LLT prescribed after statin; ezetimibe was prescribed to 7.39% of study participants upon hospitalisation, 13.9% on discharge, and 24.3% at 6 months, 31.0% at 12 months and 40.8% at 24 months after discharge from hospital (P < 0.001). Five patients were prescribed inclisiran, and four were prescribed anti-PCSK9 monoclonal antibodies (evolocumab or alirocumab). In our study, most of the patients (40.3%) were prescribed ezetimibe as second-line LLT, except for two patients. One patient was initiated on inclisiran therapy as second-line LLT for its dual benefit of lowering LDL-C and Lp (a); his LDL-C was 1.67 mmol/L, and Lp (a) was elevated at 292.1 mmol/L (normal reference < 70 nmol/L). Another patient was started on alirocumab as second-line therapy at the 24-month mark, concurrently with high-intensity statin. This patient was previously on high-intensity statin-ezetimibe combination therapy; however, ezetimibe was stopped with the initiation of PCSK-9 therapy. The prescription rates of fenofibrate and omega-3 were around 5.24% and 4.80% at 24 months, respectively, and did not change significantly over the 24-month period. According to subsequent outpatient clinical notes, 57 patients were suspected of having questionable medication adherence despite not reporting side effects from statins. Based on available documentation during follow-up appointments, approximately 16 patients were documented as non-adherent to a heart-healthy diet.

Predictors of LDL-C goal attainment

Table 3 shows the predictors of LDL-C goal attainment in our patients. Multivariate analysis showed that having a history of AMI increases the likelihood of attaining an LDL-C level < 1.4 mmol/L by 1.5 times [OR 1.57, 95% confidence interval (CI) 1.02–2.40, P = 0.040]. Factors associated with failure to achieve LDL-C levels of < 1.4 mmol/L included female gender (OR 0.58, 95% CI 0.35–0.99, P < 0.044), active smoking (OR 0.62, 95% CI 0.40–0.98, P = 0.042), prior statin use (OR 0.56, 95% CI 0.33–0.96, P = 0.034), and having higher baseline LDL-C levels (OR 0.59, 95% CI 0.48–0.73, P < 0.001). Similar predictors were found to be associated with failure to achieve LDL-C < 1.8 mmol/L, except that prior statin use was not associated with this outcome. A history of AMI was associated with an increased likelihood of achieving LDL-C < 1.8 mmol/L (OR 1.62, 95% CI 1.01–2.59, P = 0.044), whereas female gender (OR 0.50, 95% CI 0.30–0.85, P = 0.010), active smoking (OR 0.53, 95% CI 0.34–0.83, P = 0.006), and a higher baseline LDL-C levels (OR 0.52, 95% CI 0.43–0.65, P < 0.001) were factors associated with failure to achieve LDL-C < 1.8 mmol/L.

LDL-C goals attainment rates

Figure 2 shows the percentage of patients who achieved LDL-C goals at the time of hospitalisation, 6 months, 12 months, and 24 months after recruitment. At the point of recruitment, only about 12.1% and 25.6% of patients had attained the LDL-C target of < 1.4 mmol/L and < 1.8 mmol/L, respectively. Additionally, 38.9% and 55.1% of the patients achieved an LDL-C level of < 2.1 mmol/L and < 2.6 mmol/L, respectively. At the 6-month mark, there was a statistically significant increase (P < 0.001) in the proportion of patients achieving LDL-C goal < 1.4 mmol/L and < 1.8 mmol/L (21.2% and 43.0% respectively), and LDL-C goal of < 2.1 mmol/L and < 2.6 mmol/L (57.2% and 73.4% respectively). However, the LDL-C goal attainment rates plateaued after the 6-month mark, with the percentage of patients achieving LDL-C < 1.8 mmol/L

Table 3. Predictors of LDL-C goal attainment of <1.4 mmol/L and <1.8 mmol/L at any time during the follow-up period.

Variable	LDL-C <1.4 mmol/L				LDL-C <1.8 mmol/L			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Unadj. OR (95% CI)	*P*	Adj. OR (95% CI)	*P*	Unadj. OR (95% CI)	*P*	Adj. OR (95% CI)	*P*
Age (per 1 year increase)	1.01 (0.99–1.03)	0.202	0.99 (0.98–1.01)	0.482	1.02 (1.01–1.04)	0.005*	1.00 (0.98–1.02)	0.967
Female gender	0.64 (0.40–1.03)	0.065	0.58 (0.35–0.99)	0.044*	0.64 (0.41–1.00)	0.050*	0.50 (0.30–0.85)	0.010*
Race		0.020		0.219		0.030		0.544
Chinese	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
Malay	0.56 (0.37–0.84)	0.005*	0.69 (0.45–1.07)	0.095	0.55 (0.37–0.82)	0.004*	0.77 (0.49–1.20)	0.242
Indian	1.05 (0.62–1.79)	0.854	1.08 (0.61–1.91)	0.797	0.64 (0.37–1.12)	0.117	0.70 (0.38–1.28)	0.241
Others	0.59 (0.28–1.25)	0.170	0.61 (0.28–1.31)	0.203	0.79 (0.38–1.65)	0.533	0.78 (0.35–1.74)	0.548
Current smoker	0.58 (0.39–0.87)	0.008*	0.62 (0.40–0.98)	0.042*	0.49 (0.33–0.71)	<0.001*	0.53 (0.34–0.83)	0.006*
Prior statin use	1.24 (0.85–1.81)	0.259	0.56 (0.33–0.96)	0.034*	1.56 (1.07–2.26)	0.020*	0.63 (0.36–1.08)	0.091
Chronic condition								
T2DM	1.51 (1.07–2.13)	0.020*	1.39 (0.94–2.06)	0.099	0.99 (0.69–1.41)	0.952	0.77 (0.51–1.17)	0.224
Hypertension	1.23 (0.80–1.89)	0.354	0.95 (0.58–1.57)	0.847	1.38 (0.90–2.11)	0.139	1.05 (0.63–1.75)	0.841
History of AMI	1.32 (0.89–1.96)	0.161	1.57 (1.02–2.40)	0.040*	1.27 (0.83–1.92)	0.268	1.62 (1.01–2.59)	0.044*
Higher baseline LDL-C (per 1 mmol/L)	0.66 (0.56–0.77)	<0.001*	0.59 (0.48–0.73)	<0.001*	0.59 (0.51–0.69)	<0.001*	0.52 (0.43–0.65)	<0.001*

All 555 (100%) patients had available data for low-density lipoprotein cholesterol (LDL-C) and the nine explanatory variables, and were included in the multivariable analyses. *Statistically significant at $P < 0.05$. Adj.: adjusted, AMI: acute myocardial infarction, CI: confidence interval, OR: odds ratio, ref: reference, T2DM: type 2 diabetes mellitus, unadj.: unadjusted

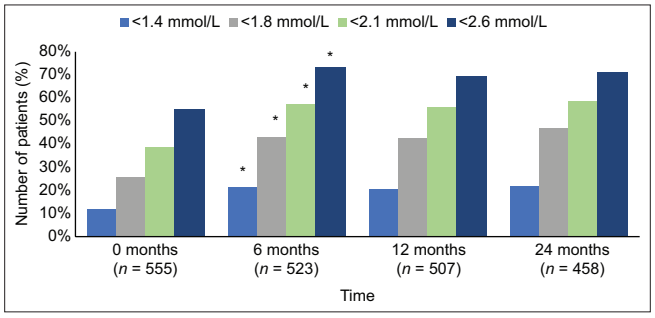

Figure 2: Graph shows percentage of patients achieving low-density lipoprotein cholesterol (LDL-C) goals at 0, 6, 12 and 24 months. *$P < 0.001$ when comparing the percentage of patients reaching LDL-C targets at 6 months against baseline (0 months). The *P* values are not shown for 12 and 24 months, as the prescriptions rates appeared similar to the prescription rates at 6 months.

plateauing at 42.8% and 47.2% at 12 and 24 months, respectively. Only 20.5% and 22.1% of patients achieved LDL-C < 1.4 mmol/L at 12 and 24 months, respectively. The highest percentage of patients (22.1%) achieving LDL-C < 1.4 mmol/L was at 24 months.

At baseline (time of hospitalisation), among patients who were on statin monotherapy (without ezetimibe or PCSK-9 agents), 85% (291/341) of the study participants did not achieve an LDL-C level < 1.4 mmol/L, while 65% (221/341) did not achieve an LDL-C level < 1.8 mmol/L. At the 6-month mark, a significant proportion of patients on statin monotherapy still did not achieve LDL-C < 1.4 mmol/L (68%, 251/368) or LDL-C < 1.8 mmol/L (43.5%, 160/358).

LDL-C and mortality

Multivariate analysis showed that attaining an LDL-C goal < 1.8 mmol/L within 12 months after hospital admission was associated with a 47% reduction in all-cause mortality (HR 0.53, 95% CI 0.30–0.94, $P = 0.030$) [Table 4]. The. LDL-C levels of < 2.1 mmol/L and < 2.6 mmol/L were also associated with a reduction in all-cause mortality (HR 0.32, 95% CI 0.17–0.61, $P = 0.001$ and HR 0.23, 95% CI 0.11–0.50, $P < 0.001$ respectively). However, an LDL-C level of < 1.4 mmol/L within 12 months after hospital admission was not associated with a statistically significant reduction in all-cause mortality, cardiovascular mortality, or MACE. An LDL-C < 2.1 mmol/L was associated with a reduction in all-cause mortality (HR 0.32, 95% CI 0.17–0.61, $P = 0.001$) and cardiovascular mortality (HR 0.33, 95% CI 0.14–0.76, $P = 0.009$), whereas LDL-C < 2.6 mmol/L was associated with a reduction in all-cause mortality (HR 0.23, 95% CI 0.11–0.50, $P < 0.001$), cardiovascular mortality (HR 0.24, 95% CI 0.08–0.68, $P = 0.007$), and MACE (HR 0.65, 95% CI 0.42–0.99, $P = 0.044$).

DISCUSSION

Our observational study shows that only about 20% of patients at very high cardiovascular risk attained an LDL-C goal of < 1.4 mmol/L by 24 months after hospital admission, with more than half of the study cohort not achieving an LDL-C goal of < 1.8 mmol/L. Our study also reports a high prescription rate of high-intensity statins (97%) for secondary prevention. Nevertheless, this was insufficient to lower LDL-C to < 1.4 mmol/L or < 1.8 mmol/L in the majority of patients. Combination therapy appears to be underutilised, with only 34% of patients on combination LLT at 24 months.

Table 4. Association of LDL-C goal attainment in patients with ischaemic heart disease with all-cause mortality, cardiovascular mortality and major adverse cardiovascular events (MACE).

Variable	Univariable Cox regression		Multivariable Cox regression	
	Unadj. HR (95% CI)	*P*	Adj. HR (95% CI)	*P*
All-cause mortality (*n*=35)				
LDL-C <1.4 mmol/L	1.13 (0.73–1.76)	0.583	0.76 (0.44–1.33)	0.339
LDL-C <1.8 mmol/L	0.85 (0.54–1.32)	0.467	0.53 (0.30–0.94)	0.030*
LDL-C <2.1 mmol/L	0.60 (0.38–0.97)	0.037*	0.32 (0.17–0.61)	0.001*
LDL-C <2.6 mmol/L	0.53 (0.29–0.98)	0.042*	0.23 (0.11–0.50)	<0.001*
Cardiovascular mortality (*n*=83)				
LDL-C <1.4 mmol/L	1.36 (0.77–2.41)	0.286	1.01 (0.51–2.00)	0.977
LDL-C <1.8 mmol/L	1.03 (0.57–1.88)	0.922	0.65 (0.31–1.36)	0.254
LDL-C <2.1 mmol/L	0.67 (0.35–1.26)	0.213	0.33 (0.14–0.76)	0.009*
LDL-C <2.6 mmol/L	0.63 (0.37–1.48)	0.291	0.24 (0.08–0.68)	0.007*
MACE (*n*=298)				
LDL-C <1.4 mmol/L	1.21 (0.96–1.53)	0.104	1.23 (0.92–1.65)	0.156
LDL-C <1.8 mmol/L	1.03 (0.81–1.31)	0.823	1.11 (0.84–1.46)	0.465
LDL-C <2.1 mmol/L	0.93 (0.71–1.23)	0.608	1.03 (0.75–1.41)	0.860
LDL-C <2.6 mmol/L	0.65 (0.45–0.93)	0.018*	0.65 (0.42–0.99)	0.044*

Lipid-lowering therapy and lipoprotein cholesterol (LDL-C) goal attainment were defined as any time within 12 months from recruitment. Multivariable Cox regression adjusted for baseline LDL-C, age at first visit, gender, race, body mass index, smoking status, medical history of hypertension, type 2 diabetes mellitus, chronic kidney disease and hospital admission for acute myocardial infarction. *Statistically significant at P <0.05. Adj: adjusted, CI: confidence interval, HR: hazard ratio, unadj: unadjusted

Interestingly, these suboptimal LDL-C goal attainments rates were almost identical to those reported in other recent large studies.[7,8,13] Earlier local studies had reported poor LDL-C goal attainment rates, ranging from 34.8% to 36.7%.[14,15] In particular, the A-SACT study in 2008 found suboptimal attainment of LDL-C targets in high-risk patients, with only 30% achieving LDL-C < 2.6 mmol/L and 6% achieving LDL-C < 1.8 mmol/L.[16] Compared with other contemporary studies, such as the GOULD registry in the United States (43.6%) and the SANTORINI registry in Europe (22.1%), our study reported a higher prescription rate of high-intensity statins.[9,13] Similar to findings from our study and another Singaporean study,[14] several large Western studies have also reported low prescription rates of combination therapy. For instance, the DA VINCI study reported that only 9% of patients were on combination therapy with ezetimibe and 1% with a PCSK-9 inhibitor,[7] while in the GOULD registry, these rates were 4.3% and 13.5%, respectively.[13] The SWEDHEART study reported that ezetimibe was initiated as add-on therapy in only 7% of patients after a follow-up visit following recruitment,[17] and the SANTORINI study showed that combination therapy was used in 24% of all patients.[8]

We observed that 6 months was a critical time point for prescription optimisation, as there were minimal changes to patients' LLTs after that point, suggesting potential barriers for both physicians and patients in altering medications when patients appear clinically stable in the outpatient setting. The European Atherosclerosis Society consensus published in 2019 recommended combination therapy with high-intensity statin and ezetimibe for very-high-risk patients to mitigate delays in LLT optimisation.[18] The LODESTAR study of 4400 Korean patients showed that a treat-to-target approach was non-inferior to an early high-intensity statin approach in reducing cardiovascular outcomes.[19] This study reported similar median LDL-C levels in patients randomised to both groups at 12 and 24 months. However, unlike randomised controlled trials, which benefit from stringent follow-ups and protocol adherence by study investigators and enrolled patients, a treat-to-target approach in real-world settings will only benefit patients if the target LDL-C is achieved within a reasonable timeframe. In our study, we observed that sequential titration of LLT, rather than initiating multiple combination LLT upfront, appeared to be the preferred method of titration. Many patients were discharged from specialist follow-up to primary care doctor after the first year or once clinically stable. There may be several challenges preventing LLT optimisation, including inertia to escalate LLT by both doctors and patients in clinically stable outpatients, as well as time constraints.[20]

Barriers to optimising LLT to achieve LDL-C goals, particularly with the use of PCSK-9 inhibitors, include medication burden, cost, administrative processes (e.g., insurance claims), physician reluctance, and patients' unwillingness to receive injections.[21,22] In our study, we observed fewer prescriptions for high doses of statins, such as atorvastatin 80 mg/day or rosuvastatin 40 mg/day (n = 46, 11.9% at 24 months), likely due to concerns about the higher prevalence of statin-associated muscle symptoms in people of Asian ancestry.[19,23,24] In a Japanese retrospective study, 32.9% of 5302 patients with ASCVD discontinued statin therapy, with 10% showing signs of possible statin intolerance within 12 months of initiation.[24]

Suspected poor medication adherence is also a likely reason for not escalating LLT, with a local study reporting up to 35% of patients being non-adherent to chronic medications, including statin therapy, and other studies reporting that at least 50% of patients are non-adherent to statin therapy within 1 year of initiation.[25,26] Ezetimibe is the most commonly prescribed non-statin LLT due to its oral administration, availability as a generic drug, and minimal side effect profile. The addition of ezetimibe to statins has been shown to lower cardiovascular mortality.[3] However, ezetimibe provides only a 15%–20% reduction in LDL-C, and further LDL-C lowering with injectable PCSK-9 inhibitors is often necessary. Barriers to prescribing PCSK-9 inhibitors, which are available only as subcutaneous injections, are also observed in other countries such as the United States, where uptake of PCSK-9 inhibitors remain low; the rate of new prescriptions among eligible patients increased only slightly from 0.5% to 3.3% despite a significant reduction in prices.[22] In our clinical practice and review of medical records, we observed that common reasons for the low prescription rate of PSCK-9 inhibitors included the cost of medication, the burden of injections, and patients' perception that additional LLT was unnecessary when they felt well as outpatients. In November 2023, the National Drug Advisory Committee listed evolocumab for subsidy under the medication assistance fund in Singapore, and this is expected to significantly increase its prescription among eligible patients.[27] Future audits will be essential to determine if this cost-subsidy strategy leads to improved LDL-C goal attainment. Additionally, the latest guidance from the local Agency for Clinical Effectiveness, released in December 2023, has now adopted an LDL-C target of < 1.4 mmol/L for all patients with a history of acute coronary syndrome, aligning local practice with international practices for LDL-C goals.[28]

Large studies have shown that for every 1 mmol/L reduction in LDL-C, there is an associated 20% reduction in major cardiovascular events, with reassuring safety data for patients achieving LDL-C < 1 mmol/L.[17,29–32] However, our study did not find that lowering LDL-C to < 1.4 mmol/L, the guideline-recommended threshold, reduced mortality in our cohort. This may be attributed to limitations such as the short study duration and small sample size. Conversely, some studies have reported that low LDL-C is associated with increased mortality in patients with coronary artery disease and acute coronary syndrome, possibly indicating underlying malnutrition.[33] A recent meta-analysis of clinical trials involving 270,288 participants showed that while high-intensity LLT was associated with a progressive reduction in cardiovascular and all-cause mortality, this trend was not observed in patients with baseline LDL-C levels < 1.8 mmol/L, suggesting that patients with higher LDL-C concentrations benefit the most from lowering of LDL-C.[34] Another study of a nationally representative sample of 19,000 US patients found a similar paradox and postulated that lower LDL-C may contribute to a higher risk of death from infection, cancer and sensory impairments, which in turn results in increased all-cause mortality.[35] This lipid paradox was also described in a study of the Singapore Myocardial Infarction Registry, which showed that low LDL-C was associated with worse outcomes in patients with ST-elevation myocardial infarction.[36] Given these conflicting data on LDL-C thresholds in ASCVD prevention, further studies are needed to determine the degree and duration of LDL-C lowering required to reduce mortality and be cost-effective in Asian patients.

Our study has certain limitations. Adherence to LLTs and the reasons for non-adherence were not captured, which prevented us from determining whether failure to achieve LDL-C goals in some patients was due to poor medication adherence. Additionally, physician inertia in intensifying LLTs was not assessed. For patients who died outside the hospital (n = 9), we were not able to access the cause of mortality from their death certificates, which may lead to an underestimation of cardiovascular mortality. However, a strength of our study lies in the thorough review of medical records and prescriptions for all LLTs, conducted as part of a contemporary observational study in patients with IHD admitted to the hospital.

In summary, our study provides contemporary data showing significant treatment gaps in lipid management among patients at very high cardiovascular risk, with 60%–80% of patients not achieving their LDL-C goals. Statin monotherapy alone appears insufficient to meet LDL-C targets in most of these patients. We found that achieving an LDL-C < 1.8 mmol/L was associated with reduced mortality over 2 years in patients with IHD requiring hospitalisation. However, larger studies are needed to determine the optimal duration of more intensive LDL-C lowering, such as LDL-C < 1.4 mmol/L or < 1 mmol/L, that would reduce mortality and be cost-effective in Asian populations. Given the proven reduction in cardiovascular mortality with lower LDL-C, more efforts are needed to rapidly improve LDL-C goal attainment in very-high-risk patients.

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Conflicts of interest

There are no conflicts of interest.

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