ORIGINAL ARTICLE

The CEPHEUS Pan-Asian survey: high low-density lipoprotein cholesterol goal attainment rate among hypercholesterolaemic patients undergoing lipid-lowering treatment in a Hong Kong regional centre

CME

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Objectives To evaluate attainment of low-density lipoprotein cholesterol goals among hypercholesterolaemic patients undergoing lipid-lowering drug treatment in Hong Kong and to identify potential determinants of treatment outcomes.

Design Cross-sectional observational study.

Setting A single site in Hong Kong, as part of the CEPHEUS Pan-Asian survey.

Patients Subjects with hypercholesterolaemia aged 18 years or above, who had been on lipid-lowering drug treatment for at least 3 months with no dose adjustment for at least 6 weeks.

Results A total of 561 such patients (mean age, 65.3; standard deviation, 9.7 years) were evaluated. Most had major cardiovascular risk factors; 534 (95.2%) of 561 patients had coronary heart disease and 534 (95.4%) of 560 patients had low-density lipoprotein cholesterol goals set at lower than 70 mg/dL. In all, 465 (82.9%) patients attained their respective low-density lipoprotein cholesterol goals. Among 75 patients who had coronary heart disease or equivalent risk, and multiple risk factors with a 10-year coronary heart disease risk of over 20%, 62 (82.7%) attained their respective low-density lipoprotein cholesterol goals. Significant predictors of low-density lipoprotein cholesterol goal attainment included the patient's baseline lipid profile (total cholesterol and low-density lipoprotein cholesterol levels), blood pressure, and drugs (statin/non-statin) used for treatment.

Conclusions Hypercholesterolaemic patients undergoing lipid-lowering drug treatment in the present Hong Kong study were able to achieve a very high attainment rate for the low-density lipoprotein cholesterol goal, despite the fact that most of them had major cardiovascular risk factors.

Key words
Anticholesteremic agents; Cardiovascular diseases/prevention & control; Cholesterol, LDL; Hypercholesterolemia; Treatment outcome

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New knowledge added by this study

- Compared to findings from other Asian studies of lipid-lowering treatment, low-density lipoprotein cholesterol (LDL-C) lowering goal attainment rates in this high-risk population were substantially greater.
- The results may be explained by the centre's treatment policy, which stipulates early and aggressive treatment and emphasises treatment compliance (by both physicians and patients).

Implications for clinical practice or policy

- Strict adherence to a lipid-lowering treatment protocol, including titration of dose and good compliance, can increase target LDL-C goal attainment in Asian patients, including those at high cardiovascular risk.

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Introduction

Hypercholesterolaemia is a major risk factor for atherosclerosis and cardiovascular disease (CVD). Its treatment, with particular emphasis on reduction and maintenance

泛亞高膽固醇血症治療情況研究（CEPHEUS）：香港一所分區醫院內有高比率的高膽固醇症患者接受降脂治療後達至低密度脂蛋白膽固醇的目標水平

目的 評估香港高膽固醇症患者接受降脂治療後其低密度脂蛋白膽固醇目標水平的達成率，並找出影響治療結果的潛在因素。

設計 橫斷面觀察研究。

安排 作為CEPHEUS泛亞研究的參與機構之一的本港一所醫院 。

患者 18歲或以上正接受降脂治療至少三個月並已連續六星期未有調整藥物劑量的高膽固醇症患者。

結果 共561名高膽固醇症患者參與研究；他們平均年齡65.3歲，標準差9.7歲。大部份患者有主要的心血管危險因素；561名患者中，534名（95.2%）有冠心病。另560名患者中，有534名（95.4%）把低密度脂蛋白膽固醇目標水平設於70 mg/dL以下。結果發現有465名（82.9%）患者能達至他們的低密度脂蛋白膽固醇目標水平。患有冠心病或相同風險，以及有多項風險因素並且其十年冠狀動脈心臟疾病的風險高於20%的75名病人中，有62名（82.7%）能達至他們的低密度脂蛋白膽固醇目標水平。達至低密度脂蛋白膽固醇目標水平的重要預測因子包括病人的基線血脂水平（總膽固醇水平及低密度脂蛋白膽固醇水平）、血壓和服食的藥物（他汀類藥物或非他汀類藥物）。

結論 縱使本研究中，大部分高膽固醇症患者都有主要的心血管危險因素，但他們能達至低密度脂蛋白膽固醇目標水平的比率相當高。

of circulating low-density lipoprotein cholesterol (LDL-C) at optimal levels, is key to reducing cardiovascular events in patients at risk.[1-3] Large, well-designed, placebo-controlled studies have demonstrated that in such patients, pharmacological intervention to lower elevated LDL-C reduces cardiovascular morbidity and mortality.[4-9] A meta-analysis of treatment outcomes in 90 056 participants from 14 randomised trials showed that statin therapy reduced the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth with every mmol/L reduction in LDL-C.[10] The impact of lipid-lowering treatment is largely dependent on the individual's baseline cardiovascular risk. Risk reduction is proportional to the amount of LDL-C lowered.[1,2,11] Guidelines for CVD prevention, such as those of the Joint European Task Force (JETF) and the US Adult Treatment Panel III guidelines of the National Cholesterol Educational Program (NCEP ATP III) on cholesterol management, have established thresholds at which lipid-lowering therapy should be initiated. These authorities have also set specific therapeutic LDL-C goals based on the individual's baseline circulating LDL-C concentrations, and the presence/absence of coronary heart disease (CHD) and other risk factors.[5,12-16]

Despite widespread availability of lipid-lowering drugs and proven beneficial outcomes of treatment, dyslipidaemia remains unsatisfactorily managed in routine clinical practice. Observational studies conducted in many parts of the world show that in real-life settings, a substantial proportion of patients undergoing pharmacological lipid-lowering treatment fail to attain target levels of LDL-C and other lipids recommended in evidence-based practice guidelines.[17-29] The recent CEPHEUS (Centralized Pan-European survey on the under-treatment of hypercholesterolaemia) conducted in eight European countries during the period 2006 to 2007[17-20] showed that only 55.3% of patients on lipid-lowering drug treatment achieved target levels recommended in the 2003 European guidelines.[30] In the United States, a follow-up study conducted from 2006 to 2007, 10 years after the first Lipid Treatment Assessment Project (L-TAP), showed that although the overall LDL-C goal attainment rate had improved by 35%, an appalling 70% of CHD patients with two or more additional risk factors still failed to attain the recommended optional LDL-C goal of <70 mg/dL.[25-27] In Asia, a recent retrospective REALITY-Asia study on hypercholesterolaemic patients undergoing statin therapy in China, Korea, Malaysia, Singapore, Taiwan, and Thailand found that only 48% of them attained NCEP ATP III–recommended LDL-C goals.[28]

Failure to attain LDL-C goals is most commonly attributed to patient non-compliance with drug treatment regimens, though poor physician adherence to treatment guidelines also plays a crucial role. Reasons for poor attainment of treatment goals can include inadequate dosing, failure to properly uptitrate the dose, not switching to a more potent drug when necessary, and a lack of follow-up after initiation of treatment. For example, the REALITY-Asia study reported that in 80% of cases, statin doses were not uptitrated, nor were there attempts to switch to a different drug despite failure to meet the LDL-C target.[28]

In Asia, comprehensive data on management of dyslipidaemia and its treatment outcomes are limited. Little is known about which CVD prevention guidelines Asian physicians use most, to what extent they follow and implement recommendations, and how well their patients fare in attaining target lipid levels. There is also a paucity of information on current treatment patterns, the profile of patients being treated, and what factors determine treatment success or failure in achieving LDL-C goals. As part of a larger Pan-Asian study, the present study sought to

find answers to the above from a patient population undergoing lipid-lowering drug treatment in Hong Kong.

Methods

Study design

This study constituted the Hong Kong part of the CEPHEUS Pan-Asian study (ClinicalTrials.gov Identifier: NCT00687492), a multinational cross-sectional observational survey of subjects on lipid-lowering pharmacological treatment in eight countries/regions. The countries/regions were: Hong Kong SAR, Indonesia, Malaysia, Philippines, Republic of Korea, Taiwan, Thailand, and Vietnam.[31] The Hong Kong part of the study was conducted at a single site, by the Division of Cardiology, Department of Medicine, Queen Mary Hospital. The study was approved by the local Institutional Review Board and conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines, and the Declaration of Helsinki. Written informed consent was obtained from all participating patients before they were enrolled into the study.

Study population

Subjects eligible for this study were hypercholesterolaemic, aged 18 years or above, and with two or more cardiovascular risk factors as defined in the updated 2004 NCEP ATP III guidelines. Also they had to have been on lipid-lowering drug treatment for at least 3 months, with no dose adjustment for a minimum of 6 weeks. Patients were ineligible if they had participated in any interventional clinical study during the preceding 90-day period, were unable or unwilling to provide informed consent, or were personally involved in the conduct of this study (eg as laboratory technicians or part of the study evaluation team).

Study objectives and endpoints

The primary objective of this study was to determine the proportion of patients on lipid-lowering pharmacological treatment attaining LDL-C goals defined by the updated 2004 NCEP ATP III guidelines.[13-15] These guidelines recommend a therapeutic LDL-C goal of <100 mg/dL for those at high risk (CHD or CHD-risk equivalents and 10-year risk >20%) of cardiovascular events, with the option to further lower the goal to <70 mg/dL for individuals at very high risk, and a LDL-C goal of 130 mg/dL for those at moderately high risk (two or more risk factors and 10-year risk of 10-20%), with an optional goal of 100 mg/dL.[13-15] Secondary objectives were: (i) to determine the proportion of patients in primary or secondary prevention, and with metabolic syndrome attaining LDL-C goals, and (ii) to identify possible determinants of treatment success or failure, including the type of drugs used, patient characteristics, and physician-related factors. The primary endpoint of the study was the LDL-C goal attainment rate, defined as the proportion of patients on lipid-lowering pharmacological treatment achieving their respective therapeutic LDL-C goals in the study population. The secondary endpoints included LDL-C goal attainment rates in various sub-groups of patients stratified by primary and secondary prevention, different cardiovascular risk profiles, statin/non-statin drug treatments, identification of the determinants of goal attainment, and the impact of such goals on physician prescribing of lipid-lowering drugs.

Study procedure

This was a single-visit study. There was no selection of physician-investigators. All 13 cardiologists at the Hong Kong centre were invited to participate, and all joined the study. No endocrinologists, general practitioners, primary care, or other type of physician participated in this Hong Kong study. On commencement, each physician-investigator completed a physician questionnaire that comprised 23 questions designed to collect information on their awareness and use of practice guidelines, therapeutic LDL-C goals adopted, management practice of hypercholesterolaemia, and relevant communications with patients. Consenting patients were then consecutively enrolled and assessed. Participating patients completed the patient questionnaire, which comprised 17 questions designed to explore their perceptions of hypercholesterolaemia and its management, adherence to the prescribed treatment regimen, and personal satisfaction with the treatment. The patient was then assessed by the physician.

Demographic and other clinically relevant information, including cardiovascular medical history such as family history of premature CHD, the presence of known cardiovascular risk factors, including CHD or CHD-risk equivalents (metabolic syndrome, smoking habits, past lipid profile if available) were retrieved, as were current lipid-lowering therapy and reason for treatment. The cardiovascular risk level and therapeutic LDL-C goal of each patient were then classified according to definitions and criteria set by the updated 2004 NCEP ATP III guidelines, as described above.[13-15] An overnight fasting blood sample was drawn from each patient to determine blood glucose and lipid (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], and triglyceride [TG]) concentrations. The sample analysis was performed at the hospital laboratory using standard biochemical analytical methods.

Statistical considerations

For the Pan-Asian CEPHEUS study, sample size was determined with the intention of ensuring that the proportion of subjects reporting on the primary endpoint should be estimated with sufficient precision to cope with the heterogeneity of the population. Thus, a target sample size of 8000 patients at 850 to 1600 patients per country was determined. This would allow the proportion of subjects for reporting on the primary endpoint to be estimated with 95% confidence intervals (CIs) between ±2.4% and ±3.4%. For the present evaluation, the full dataset comprised 564 patients enrolled by the participating physician-investigators at the Hong Kong study site. All analyses were performed on the per-protocol population set, which consisted of 561 consenting patients who completed the single-visit study, and whose attending physicians completed and returned the physician questionnaire. Where there were unknown or missing data, the analyses were performed only on the evaluable set of data.

Descriptive statistics including frequency distributions, medians, means and standard deviations (SDs) were used to describe demographics, anthropometric measurements (body weight, height, and waist circumference), and concentrations of total cholesterol, LDL-C, HDL-C, and TG. The LDL-C goal attainment rate was expressed as the percentage of patients achieving their goals, together with 95% CI. To determine factors affecting achievement of LDL-C goals, factors to be identified were grouped into two categories: patient determinants and physician determinants. Patient factors were screened in a univariate analysis by means of logistic model analysis. Physician factors were screened in a univariate analysis by means of generalised linear mixed model analysis with a random effect of physician using the NLMIXED procedure of the SAS system (SAS Institute Inc., Cary [NC], US). Regression coefficient estimate, standard error and P value for each effect, as well as estimated odds ratio (OR) with associated 95% CI were computed.

Factors with P values of <0.10 in these univariate analyses were further evaluated using a multivariate approach by means of the generalised linear mixed model stated above. Variables were chosen and added to the model one by one in each step, until no candidate variables with a P value of <0.05 remained.

Results

Between 28 April and 31 December 2008, all 13 physician-investigators from the single study site in Hong Kong (the Division of Cardiology, Queen Mary Hospital) were involved. In all, 561 (99%) of 564 patients who completed the single-visit study formed the per-protocol population for statistical evaluation of the endpoints. These were patients who returned the patient survey questionnaire, and whose attending physicians returned the physician survey questionnaire.

Demographics and practice characteristics of physicians

Among the 13 physicians (all cardiologists) who answered and returned the physician survey questionnaire, 10 (77%) were males, and their mean ± SD duration of time in practice was 13 ± 8 (range, 4-29) years. The mean (± SD) age of the 11 participating physicians who provided their ages was 37 ± 9 years. All 13 participating physicians stated that they used blood LDL-C concentration as the laboratory measure of treatment outcome and followed clinical practice guidelines to establish therapeutic targets for their patients. Among them, they had individual cholesterol targets set for 74% of their hypercholesterolaemic patients, and 10 (77%) of them reviewed their patients once every 6 months. Nine of the physicians evidently used 'national' CVD prevention practice guidelines which, in the context of this single-centre study, were inferred to mean the hospital formulary protocol; only three (33%) of them also used the US NCEP ATP III guidelines and/or the JETF guidelines.

Patient demographics and baseline characteristics

Demographics and baseline characteristics of the patients included in the final analysis, including primary diagnoses and CVD risk categories, are shown in Table 1. The total number of patients evaluated comprised 404 (72.0%) males and 157 (28.0%) females. Among them, 560 patients provided information on their age, which averaged 65.3 years (SD, 9.7; median, 67 years), with most (85%) being over 55 years. A total of 541 (96.8%) of 559 patients were in the age category stratified as having higher risk for developing CVD (men, ≥45 years; women, ≥55 years). In all, 352/561 (62.7%) of the patients had abdominal obesity, defined as having a waist circumference of >90 cm in men or >80 cm in women. Mean body mass index (BMI) computed for the 560 patients with anthropometric data was 25.9 ± 3.9 kg/m^2. Among these patients, 225 (40.2%) were overweight (BMI, 25 to <30 kg/m^2), while 88 (16%) were obese (BMI, ≥30 kg/m^2). Blood pressure was measured in 558 patients; the mean systolic blood pressure was 132 ± 20 mm Hg, and the mean diastolic blood pressure was 75 ± 12 mm Hg. Based on the 2004 updated NCEP ATP III guidelines, most patients were considered to be at very high risk for CVD; 534/559 (95.5%) of the patients fulfilled the criteria for the very high risk category (established CHD plus multiple major risk factors, severe and persistent risk factors, multiple

TABLE 1. Demographic and baseline characteristics of patients (n=561)

Characteristic*	No. (%) of patients†
Age (years)	65.3 ± 9.7‡
Gender	
Male	404 (72.0)
Female	157 (28.0)
CHD risk factors	
Cigarette smoking (any in past month)	62 (11.1)
Hypertension (>140 / >90 mm Hg or on antihypertensive medication)	418 (74.5)
Low HDL-C (<40 mg/dL)	87 (15.5)
Family history of premature CHD (first-degree relative with clinical CHD or sudden death age <55 years in men or <65 years in women)	72 (12.8)
Age (men ≥45 years; women ≥55 years)	541 (96.8)
High HDL-C (≥60 mg/dL) [negative risk factor]	15 (2.7)
CHD or CHD-risk equivalents	
CHD	534 (95.2)
Peripheral arterial disease	20 (3.6)
Carotid artery disease	0
Abdominal aortic aneurysm	0
Diabetes	230 (41.0)
Multiple risk factors with 10-year risk for CHD >20%	75 (13.5)
Metabolic syndrome	279 (49.9)

* CHD denotes coronary heart disease, and HDL-C high-density lipoprotein cholesterol
† Percentages and summary statistics are based on patients in per-protocol set with non-missing data
‡ Mean ± standard deviation

risk factors of metabolic syndrome or acute coronary syndrome), while 75/557 (13.5%) of the patients had multiple risk factors with a 10-year risk for CHD >20%. The majority of the 561 patients had CHD or CHD-risk equivalents or other major risk factors; 534 (95.2%) had CHD, 20 (3.6%) had peripheral arterial disease (PAD), 230 (41.0%) had diabetes, 418 (75%) had hypertension, and 72 (13%) had a family history of premature CHD. In addition, based on evaluable data, 279/559 (49.9%) had metabolic syndrome. In terms of other risk factors, 174/561 (31.0%) had blood TG levels of ≥150 mg/dL, 312/556 (56.1%) had fasting blood glucose levels of ≥100 mg/dL, and 87/561 (15.5%) had low HDL-C levels of <40 mg/dL. At the time of the survey, 62/561 (11.1%) of the patients declared that they were smokers (Table 1).

Therapeutic low-density lipoprotein cholesterol goals and drugs used in treatment

Information on LDL-C goals and lipid-lowering drug treatment is presented in Table 2. Based on the 2004 updated NCEP ATP III guidelines, the majority of the 560 patients for whom treatment goal was recorded had their therapeutic LDL-C goal set at <70 mg/dL, which is the optional goal recommended for

TABLE 2. Low-density lipoprotein cholesterol goals and lipid-lowering drug treatment of patients

Characteristic*	No. (%) of patients†
LDL-C goal according to 2004 updated NCEP ATP III (n=560)	
<70 mg/dL	534 (95.4)
<100 mg/dL	13 (2.3)
<130 mg/dL	13 (2.3)
Period on treatment (years) [n=323]	3.6 ± 2.7‡
Reason for prescribing LLD (n=560)	
Primary prevention	21 (3.8)
Secondary prevention	538 (96.1)
Familial hypercholesterolaemia	1 (0.2)
Type of LLD (n=561)	
Single LLD therapy	560 (99.8)
Statins monotherapy	555 (98.9)
Fibrates monotherapy	5 (0.9)
Other monotherapy	0
Multiple LLD therapy	1 (0.2)

* LDL-C denotes low-density lipoprotein cholesterol, NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III, and LLD lipid-lowering drug
† Percentages and summary statistics are based on patients in final analysis set with non-missing data
‡ Mean ± standard deviation

individuals at very high cardiovascular risk; that is, 534 (95.4%) had goals set at <70 mg/dL, 13 (2.3%) had goals set at <100 mg/dL, and 13 (2.3%) had goals set at <130 mg/dL. Of the 560 patients with CVD risk and ongoing drug treatment data, 538 (96.1%) were treated for secondary prevention, 21 (3.8%) for primary prevention, and only one patient was treated for familial hypercholesterolaemia. The drug treatment history gathered from 323 patients showed that they had been on lipid-lowering drug treatment for a mean duration of 3.6 (SD, 2.7; range, 0-13) years. There was little change in drug prescription after initiation of therapy. At enrolment to this study, 440/554 (79.4%) of the patients were still taking the same dose of the same lipid-lowering drug first prescribed. Whereas 71 (12.8%) of them had their drug changed once or twice by their physician, 34 (6.1%) were taking the same drug at an increased dose, and only 9 (1.6%) had had their drug changed several times.

Notably, 560/561 (nearly 100%) of the patients were on monotherapy and in 555 (98.9%) it was a statin. The most commonly used statin was simvastatin (for 343 [61.8%] of the patients on statin monotherapy), followed by atorvastatin (for 124 [22.3%] of the patients), and rosuvastatin (for 86 [15.5%] of the patients). The most frequently prescribed daily dosage was <20 mg of simvastatin (to 216 [38.6%] of the patients), followed by 10 mg of atorvastatin (to 61 [10.9%] of the patients), and 10 mg of rosuvastatin (to 41 [7.3%] of the patients). Very few patients were on other classes of lipid-lowering drugs, whether used singly or in combination with statins or other drugs. Only 5/561 (0.9%) of the patients were taking fibrates, one was on combination therapy (statin with fibrate); no patient was in receipt of any other type of monotherapy.

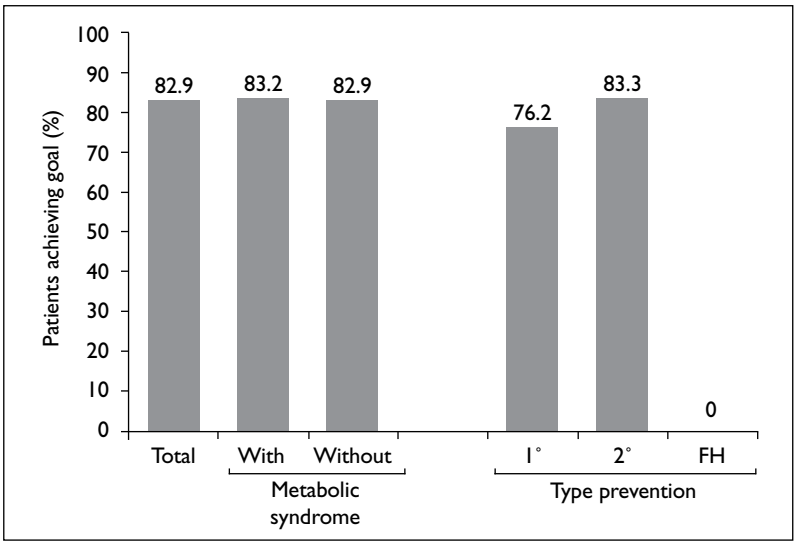

FIG 1. Attainment of low-density lipoprotein cholesterol goals among patients treated for primary and secondary prevention, with or without metabolic syndrome
1° denotes primary prevention, 2° secondary prevention, and FH familial hypercholesterolaemia

Treatment outcomes

Based on available last known lipid profiles before initiation of lipid-lowering drug treatment, mean blood concentrations of total cholesterol, LDL-C, HDL-C, and TG were 216 ± 48 mg/dL (n=231), 137 ± 45 mg/dL (n=230), 45 ± 10 mg/dL (n=231), and 170 ± 110 mg/dL (n=231), respectively. The corresponding concentrations measured at enrolment to this study after the patients had been on lipid-lowering drug treatment for at least 3 months were 156 ± 30 mg/dL (n=561), 84 ± 24 mg/dL (n=560), 44 ± 11 mg/dL (n=561), and 141 ± 95 mg/dL (n=561). Overall, 465/561 (82.9%) of patients attained the therapeutic LDL-C goals recommended by the 2004 updated NCEP ATP III guidelines. Those who reached their target levels included 343/404 (84.9%) males and 122/157 (77.7%) females. Target LDL-C goals were attained by 16/21 (76.2%) of patients treated for primary prevention, and 448/538 (83.3%) treated for secondary prevention (Fig 1). The only patient with familial hypercholesterolaemia failed to attain the target LDL-C level.

The proportions of patients attaining each LDL-C goal, based on risk category, are shown in Figure 2a. The LDL-C goal attainment rate was high across all risk-stratified categories, but highest in those whose goal was set at <100 mg/dL; all 13 (100%) patients in this category achieved the target LDL-C level. In the largest category of patients, with target LDL-C level set at <70 mg/dL, 444/534 (83.1%) achieved the target LDL-C level. The goal attainment rate was lowest in patients whose LDL-C goal was set at <130 mg/dL, only 7/13 (53.8%) of whom attained their target level.

The LDL-C goal attainment rate was high even in patients classified as at very high cardiovascular risk by the 2004 updated NCEP ATP III guidelines. Among 75 patients who had CHD or CHD-risk equivalent, and multiple risk factors with a 10-year CHD risk of >20%, 62 (82.7%) attained their LDL-C goal, which was virtually the same as the 82.8% attained by 399 of 482 patients not at high risk. Among patients with metabolic syndrome, 232/279 (83.2%) patients attained their LDL-C goals (Fig 1), which was nearly the same as in the 232/280 (82.9%) of patients who did not have metabolic syndrome. Among 272 patients presenting with metabolic syndrome and low HDL-C, 239 (87.9%) attained their LDL-C goals, which was much higher than that achieved by those without low HDL-C levels. Among the latter, only 226/288 (78.5%) managed to reach their respective target LDL-C levels. In contrast, the rate among patients with high blood pressure (≥130 / ≥85 mm Hg) was lower than that achieved by patients without high blood pressure, the respective rates being 222/282 (78.7%) and 243/279 (87.1%). Among patients with diabetes, 201/230 (87.4%) attained their LDL-C goals, which

was, surprisingly, much higher than the 79.8% goal attainment rate achieved by 264 of the 331 patients who did not have diabetes. Among patients with other major risk factors, 354/418 (84.7%) with hypertension, 445/534 (83.3%) with CHD, 15/20 (75.0%) with PAD, and 55/72 (76.4%) with a family history of premature CHD attained their respective LDL-C goals.

Determinants of drug prescriptions and low-density lipoprotein cholesterol goal attainment

In terms of patient factors, univariate analysis using logistic regression models found the following characteristics to be significant predictors for attainment of LDL-C goals: gender, age, baseline total blood cholesterol and LDL-C concentrations, the LDL-C goals themselves, high systolic and diastolic blood pressure, diabetes, or low HDL-C. The predictability OR and 95% CI of factors significantly associated with the attainment of 2004 updated NCEP ATP III-recommended LDL-C goals are shown in Table 3.

The most significant patient-related predictors of LDL-C goal attainment were baseline total cholesterol and LDL-C concentration, and blood pressure (systolic and diastolic). Higher baseline total cholesterol and LDL-C concentrations were associated with significantly lower odds of attaining LDL-C goals (P<0.001). The likelihood of attaining a goal decreased with increasing baseline LDL-C (OR=0.98; 95% CI, 0.97-0.99 for every 100 mg/dL increment) or total cholesterol level (OR=0.99; 95% CI, 0.98-0.99 for every 100 mg/dL increment). Similarly, the likelihood of attaining LDL-C goals was lower in patients with higher systolic blood pressure (OR=0.98; 95% CI, 0.97-0.99 for every 10 mm Hg increment; P=0.002), and with higher diastolic blood pressure (OR=0.97; 95% CI, 0.95-0.99 for every 10 mm Hg increment; P=0.002). Baseline BMI, HDL-C, and TG levels were not found to be significant predictors of LDL-C goal attainment. However, being female decreased the odds of attaining the goals (OR=0.62; 95% CI, 0.39-0.99; P=0.043), while older age increased the odds (OR=1.02; 95% CI, 1.00-1.05 for every 10 years increment in age; P=0.038) [Table 3].

Physician characteristics that were significant determinants of LDL-C goal attainment included: the physician's gender (OR=0.31; 95% CI, 0.14-0.70; female vs male, P=0.009), years of experience (OR=1.37; 95% CI, 1.01-1.87; continuous variable, P=0.046), use of HDL-C as the lipid parameter measurement used to inform the patient (OR=1.90; 95% CI, 1.10-3.28; yes vs no, P=0.026), use of TG as the lipid parameter measurement to inform the patient (OR=1.91; 95% CI, 1.08-3.39; yes vs no, P=0.030), and whether or not the physician tended to prescribe a lipid-lowering drug only to patients who had proved they could adhere to diet and exercise (OR=5.64; 95% CI, 3.00-10.63; highest vs lowest grade; P<0.001) [Table 3]. The patient's LDL-C goal was found to be a significant predictor of the physician's prescription of lipid-lowering drugs. Compared to those whose goal was set at <70 mg/dL, patients whose goal was set at <100 mg/dL had a lower chance of being prescribed a statin by his/her attending physician (OR=0.09; 95% CI, 0.01-0.87; P=0.038). This infers that the more stringent the LDL-C goal, the more likely it was that a patient would be prescribed a statin by the physician.

On multivariate analysis, factors significantly (negatively) associated with the attainment of 2004 updated NCEP ATP III–recommended LDL-C goals were: higher LDL-C level before drug treatment (per 100 mg/dL), high blood pressure (≥130 / ≥85 mm Hg), patient being uninformed about the cholesterol level, and female gender (Table 4). Among these, the strongest predictor of LDL-C goal attainment was the baseline LDL-C level.

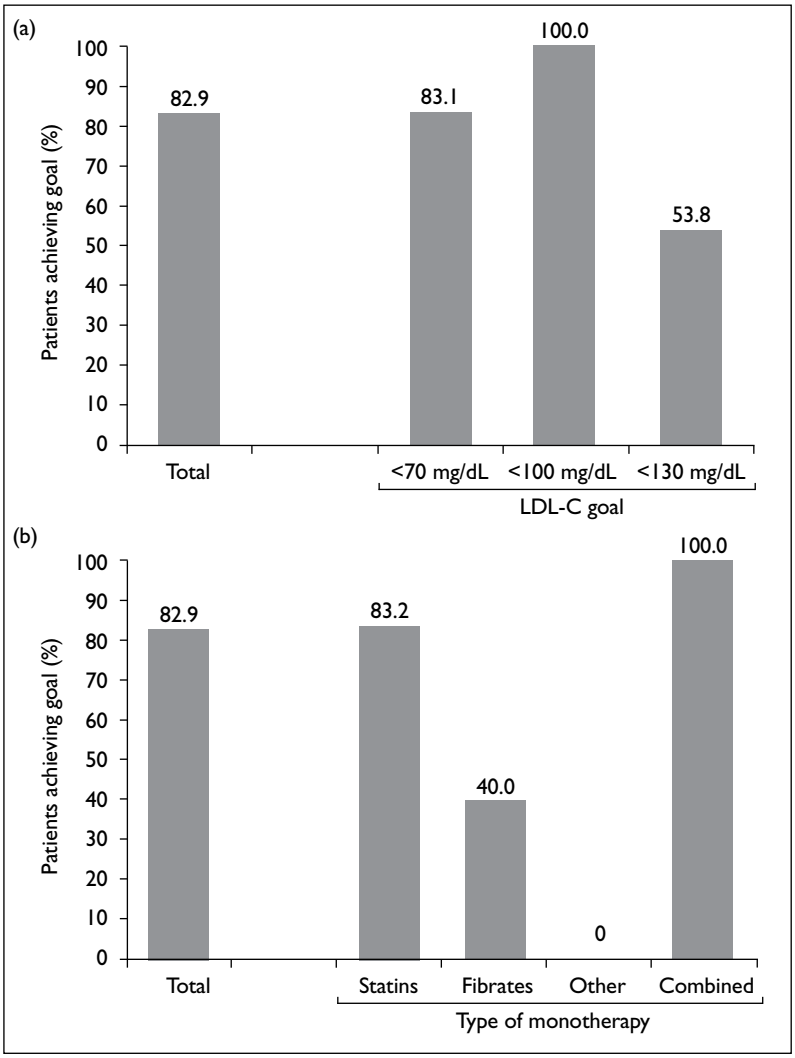

FIG 2. Proportions of patients attaining 2004 updated National Cholesterol Educational Program Adult Treatment Panel III–recommended low-density lipoprotein cholesterol (LDL-C) goals based on (a) risk category and (b) various lipid-lowering drug therapies

TABLE 3. Factors significantly associated with the attainment of 2004 updated National Cholesterol Education Program Adult Treatment Panel III–recommended low-density lipoprotein cholesterol goals (univariate analysis)*

Variable†	OR	95% CI	P value‡
Patient and patient-related characteristics			
LDL-C goal			
100 mg/dL vs 70 mg/dL§	-	-	0.011
130 mg/dL vs 70 mg/dL	0.24	0.08-0.72	-
Total cholesterol before drug treatment (per 100 mg/dL)‖	0.99	0.98-0.99	<0.001
LDL-C before drug treatment (per 100 mg/dL)‖	0.98	0.97-0.99	<0.001
Age (per 10 years)‖	1.02	1.00-1.05	0.038
SBP (per 10 mm Hg)‖	0.98	0.97-0.99	0.002
DBP (per 10 mm Hg)‖	0.97	0.95-0.99	0.002
Gender			
Female vs male	0.62	0.39-0.99	0.043
CHD or CHD-risk equivalent, diabetes			
Yes vs no	1.76	1.10-2.82	0.019
HDL-C (men <40 mg/dL; women <50 mg/dL) [component of metabolic syndrome]			
Yes vs no	1.99	1.25-3.15	0.003
High blood pressure (≥130 / ≥85 mm Hg) [component of metabolic syndrome]			
Yes vs no	0.55	0.35-0.86	0.009
Drug treatment factors			
Type of monotherapy (excluding 1 patient on combination therapy)			
Fibrate vs statin monotherapy	0.13	0.02-0.81	0.029
Statin monotherapy and dose (including only 3 major statin monotherapies)			<0.001
Rosuvastatin 10 mg vs 5 mg	1.07	0.26-4.35	
Rosuvastatin >10 mg vs 5 mg	0.37	0.08-1.77	
Atorvastatin 5 mg vs rosuvastatin 5 mg	1.70	0.29-10.16	
Atorvastatin 10 mg vs rosuvastatin 5 mg	1.66	0.41-6.68	
Atorvastatin >10 mg vs rosuvastatin 5 mg	0.18	0.05-0.63	
Simvastatin <20 mg vs rosuvastatin 5 mg	0.92	0.30-2.81	
Simvastatin 20 mg vs rosuvastatin 5 mg	0.68	0.21-2.19	
Simvastatin >20 mg vs rosuvastatin 5 mg	0.33	0.09-1.27	
Physician characteristics			
Physician's gender			
Female vs male	0.31	0.14-0.70	0.009
Physician's years of practice‖	1.37	1.01-1.87	0.046
Type of lipid parameters measurement physician used to inform the patient: HDL-C			
Yes vs no	1.90	1.10-3.28	0.026
Type of lipid parameters measurement physician used to inform the patient: TG			
Yes vs no	1.91	1.08-3.39	0.030
Physician tends to prescribe a LLD only to patients who have proved they could adhere to diet and exercise (ordinal variable ranged from '1: disagree strongly' to '5: agree strongly', but only 3 categories observed)			
3 vs 1	5.77	1.27-26.25	<0.001
4 vs 1	5.64	3.00-10.63	

* LDL-C denotes low-density lipoprotein cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure, CHD coronary heart disease, HDL-C high-density lipoprotein cholesterol, TG triglyceride, LLD lipid-lowering drug, OR odds ratio, and CI confidence interval

† The results for patient-related characteristics and drug treatment factors are based on univariate logistic model analysis, and the results for physician characteristics are based on the generalised linear mixed effect model analysis. The results for continuous variables are per 10 or 100 units of changes (this number of "100" was used not from a clinical perspective, but rather for obtaining stable results in statistical computation using generalised linear mixed model)

‡ The P values are for the overall effect of each factor, rather than for individual comparisons within a factor

§ Statistics could not be computed due to 100% achievement of LDL-C goals

‖ Continuous variable

TABLE 4. Factors significantly associated with the attainment of 2004 updated National Cholesterol Education Program Adult Treatment Panel III–recommended low-density lipoprotein cholesterol goals (multivariate analysis) [n=229]*†

Variable	Regression coefficient estimate	SE	OR	95% CI	P value
LDL-C before drug treatment (per 100 mg/dL)					
Continuous variable	-1.838	0.442	0.16	0.06-0.43	<0.001
High blood pressure (≥130 / ≥85 mm Hg)					
Yes vs no	-1.134	0.418	0.32	0.13-0.83	0.007
PQ3: Patient informed about the cholesterol level					
Yes vs no	-1.087	0.401	0.34	0.14-0.84	0.007
Patient gender					
Female vs male	-0.881	0.405	0.41	0.17-1.04	0.031

* The results for the multivariate analysis are based on the generalised linear mixed effect model analysis with a random effect of investigator

† LDL-C denotes low-density lipoprotein cholesterol, PQ3 Patient Questionnaire 3, SE standard error, OR odds ratio, and CI confidence interval

The type of therapy and type of monotherapy employed, and the drug and dose used were significant predictors of LDL-C goal attainment. The proportions of patients on various lipid-lowering drug therapies attaining recommended LDL-C goals are shown in Figure 2b. Patients who were on statin monotherapy had the highest goal attainment rate of 462/555 (83.2%). While 463/556 (83.3%) of those on statins administered singly or in combination with another drug attained their LDL-C goals, only 2/5 (40.0%) on non-statin therapies did so. Compared to patients on statin therapy, the OR for attaining LDL-C goals in those on non-statin therapy was only 0.13 (95% CI, 0.02-0.81; P=0.029). In the present study, however, the number of patients in the non-statin group was very small.

In the population studied, personal compliance with drug treatment regimens, determined by how often the patients forgot to take their medications, did not seem to have an impact on LDL-C goal attainment (P=0.064). The majority of patients in this population demonstrated good compliance with drug treatment; in terms of the "frequency tablet(s) were forgotten" question, only 14/257 (5.4%) admitted that they forgot to take their tablet more than once a week, whilst 181/257 (70.4%) rarely forgot their tablet (once a month or less). A vast majority of patients comprising 538/559 (96.2%) claimed they "always took tablet daily to lower cholesterol". In addition, only 49/552 (8.9%) patients thought that missing their daily tablet(s) more than once a week would not affect their cholesterol levels, suggesting that most patients were aware of the importance of drug treatment in the management of their hypercholesterolaemia.

Discussion

Thus far, most studies evaluating the outcome of lipid-lowering drug treatment in hypercholesterolaemic patients in real-life settings have shown unsatisfactory treatment results, with a high proportion of patients failing to attain recommended LDL-C goals.[25-29,31,32] In Asia, several studies, including the recent multinational REALITY-Asia study conducted in six Asian regions, showed that a high proportion of Asian hypercholesterolaemic patients—in particular, those in the higher cardiovascular risk categories—were not attaining their therapeutic LDL-C goals.[28,29,31,32] That study found that only 48% of the 2622 patients across all cardiovascular risk categories evaluated attained NCEP ATP III–recommended LDL-C goals.[28] In another study conducted in Hong Kong, a retrospective analysis of hospital records of lipid-lowering drug treatment in 196 adult patients (mostly with CHD or CHD-risk equivalent) reported that 44% of the patients failed to attain their LDL-C goals after 1.9 years of treatment.[29] Yet another study conducted on 5174 survivors of acute myocardial infarction or coronary revascularisation in Singapore found that approximately 70% were unable to attain the LDL-C goal of <100 mg/dL.[32]

Against this background of dismal findings, the high LDL-C goal attainment rate we found in this Hong Kong study seems exceptionally high and surprising. In the present study, 82.9% of 561 patients successfully attained their LDL-C goals recommended in the 2004 updated NCEP ATP III guidelines. This was despite the fact that the vast majority of these patients were at very high cardiovascular risk; 96% (534/559) of the patients fulfilled the criteria for being in the very high risk category, and 95% (534/561) had CHD. Moreover, most patients (95%; 534/560) had their therapeutic LDL-C targets set at the most stringent level of <70 mg/dL. The high LDL-C goal achievement rate in this population of largely very high risk patients defied findings reported by previous studies that suggested a lower likelihood of goal attainment

in such patients.[28,31] More striking still was the very small difference in the goal attainment rate between patients with and without certain major risk factors (including some of the most serious risk factors such as CHD). In some cases, the goal attainment rate was better in the patients presenting with this risk factor than without. However, we are aware that such a comparison may be statistically skewed due to inequality in the sizes of the groups being compared, since the majority of the patients had CHD or a CHD equivalent, and those without were a minority. Nevertheless, this exceptionally high level of LDL-C goal attainment rate was rare in Asia. It was surpassed only by a finding from the American-led multinational L-TAP 2 study, which reported a goal attainment rate of 84% among 983 treated patients in Korea.[26,27] However, this Korean population studied differed from ours in that most were at lower cardiovascular risk; only 54% had CHD compared to 95% in our cohort. However, results from both studies demonstrated that an excellent LDL-C goal attainment rate is achievable in Asian patients on lipid-lowering treatment. The high goal attainment rate in our study could in part be explained by the efficient clinical plan that was in place at our centre, which utilises an early and aggressive treatment protocol.[33]

Significant predictors of therapeutic LDL-C goal attainment included the type of therapy and type of monotherapy employed, and the drug and dose used for treatment. Patients on statin monotherapy were most likely to attain their goals; 83% (462/555) did so compared to only 40% (2/5) on non-statin therapy (P=0.029). The goal attainment rate achieved with statins was much higher than that reported by the Pan-European CEPHEUS study, which also demonstrated that, compared to other drugs, statin therapy resulted in the highest rate of LDL-C goal attainment.[17] In that study, however, for patients treated with statin monotherapy, the LDL-C goal attainment rate was 57% (vs 83% in this study).[17] It should be noted that the majority of patients (99%; 555/561) in our study were on statin monotherapy, and this could influence the statistics for comparison of goal attainment.

Little change in drug treatment was noted since initiation of lipid-lowering therapy. Soon after enrolment, 79% (440/554) of patients continued to take the same dose of the same lipid-lowering drug first prescribed to them; only 71 (13%) had their drug changed once or twice. At first glance, it might appear that there was a lack of follow-up dose adaptation. Studies conducted elsewhere have shown that suboptimal use of drugs is a potential cause of failure to attain lipid goals. This was thought to be the case in the Centralized Pan-European CEPHEUS study, where the overall rate of LDL-C goal attainment was only 55% although 93% of the patients were taking statins.[17] That study found that physicians only changed the drug and/or dose in 40% of the patients. In contrast, most patients in our present study managed to achieve their LDL-C goals despite being maintained at their initial dose (most commonly <20 mg for simvastatin, 10 mg for atorvastatin, and 10 mg for rosuvastatin). This shows that the dosages of drugs given were sufficient to control LDL-C levels, even in patients at very high cardiovascular risk. Indeed, multiple past studies have indicated that in Asians, the effective statin dose might not be as high as that needed for Caucasians.[34-39] A huge open-label study of simvastatin in 51 321 hypercholesterolaemic patients demonstrated that, for Japanese, an initial 5 mg dose was as effective as the 20 mg dose used by Caucasians.[35] In the present study, simvastatin was the most commonly used statin, and the most common dose administered was 20 mg, the same dose commonly administered to Caucasians. This suggests that uptitrating from the initiating drug doses was probably not an issue in our population, and might not even be warranted. Many attending physicians seemed aware of this due to their long experience in the field. Thus, in most cases, the reason for Asian patients failing to achieve LDL-C goals could lie elsewhere.

One of the most commonly cited reasons for failure to attain target LDL-C levels is poor adherence to drug treatment. Adherence could involve both physician adherence to CVD practice guidelines and the patient compliance with drug treatment. In our study, both were demonstrated to be excellent. All physicians declared that they followed clinical practice guidelines to establish therapeutic targets, and such targets were set for most (74%) of their hypercholesterolaemic patients. In addition, 77% of the physicians stated that they reviewed their patients once every 6 months. The majority of patients in this study population were compliant with drug treatment. Based on the survey questionnaire returned, 96% (538/559) of the patients claimed that they "took their tablet daily to lower cholesterol" and only 5% (14/257) of them admitted that they "forgot to take their tablet more than once a week". Such excellent adherence demonstrated by both physicians and patients may have contributed in no small part to the exceptional LDL-C goal attainment rate achieved.

Physician gender and years of experience were two significant predictors of LDL-C goal attainment in the univariate analysis. The physicians in this study could be considered very experienced as they had been in practice for a mean of 13 years. Their long experience in the field of cardiology surely helped them to determine the best therapeutic approaches and disease management strategies to achieve optimal treatment outcomes. From the patient's perspective, baseline blood pressure,

total cholesterol and LDL-C levels were the most significant, albeit negative, predictors of LDL-C goal attainment in univariate analysis. Higher pre-treatment LDL-C levels and high blood pressure were also negative predictors in the multivariate analysis. For patients in this study, however, the mean systolic blood pressure (132 ± 20 mm Hg), mean diastolic blood pressure (75 ± 12 mm Hg), mean total cholesterol (216 ± 48 mg/dL) concentration, and mean LDL-C (137 ± 45 mg/dL) concentration were not particularly high, and therefore not expected to have a large impact on goal attainment. Two other significant predictors of LDL-C goal attainment were the patient age and gender. Patients who were female and younger had lower odds of attaining treatment goals. Female gender was also a negative predictor of LDL-C goal achievement on multivariate analysis. The median age of patients in this study was 67 years, 85% were aged over 55 years, and 72% were males, all of which might help explain, at least in part, the high degree of goal attainment in our patients.

The above inferences notwithstanding, the results of this study should be interpreted within the context and limitation of the study design and setting. Most notably, the population studied was from a single site. The exclusion of patients 'unwilling' to provide informed consent may have resulted in some self-selection bias, as it is unclear whether those who were 'willing' might have been systematically different from the 'unwilling'. The cohort of patients under study might not be representative of the intended study population at large, particularly as the study site was a cardiology specialty centre, and there were no patients treated by endocrinologists, general practitioners, or primary care physicians. All the physicians at this centre were well-trained and experienced in managing dyslipidaemia in high-risk patients, and so their practice might have been more sophisticated than in average practices. Furthermore, our survey questionnaires, which were not pre-validated, were developed only for exploratory purposes. Moreover, the survey was designed to collect limited information, and may have missed addressing many other co-determinants of LDL-C goal attainment in the target population.

Conclusions

Hypercholesterolaemic patients undergoing lipid-lowering drug treatment in our Hong Kong centre were able to achieve very high LDL-C goal attainment rates. This was despite most patients having CHD or CHD-risk equivalents, or other major risk factors, many of whom were targeted to attain the lowest LDL-C goal of <70 mg/dL. Good management strategies, appropriate therapeutic approaches, and good patient and physician adherence to recognised practice guidelines could have played crucial roles in achieving these outcomes.

Declaration

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