Original Article

Suboptimal Control of Lipid Levels: Results from 29 Countries Participating in the Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolaemia (CEPHEUS)

Chern-En Chiang[1], Jean Ferrières[2], Nina N Gotcheva[3], Frederick J Raal[4], Abdulla Shehab[5], Jidong Sung[6], Karin M Henriksson[7, 8] and Michel P Hermans[9]

[1]General Clinical Research Center, Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan
[2]Department of Cardiology, Toulouse University Hospital, Toulouse, France
[3]Department of Cardiology, National Heart Hospital, Sofia, Bulgaria
[4]Faculty of Health Sciences, Johannesburg Hospital, Johannesburg, South Africa
[5]Department of Internal Medicine, United Arab Emirates University, Al-Ain, United Arab Emirates
[6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[7]AstraZeneca Gothenburg, Mölndal, Sweden
[8]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[9]Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, Brussels, Belgium

***Aim*: Five multicentre, cross-sectional Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolaemia (CEPHEUS) were conducted in 29 countries across Asia, Western Europe, Eastern Europe, the Middle East, and Africa. The surveys assessed the current use and efficacy of lipid-lowering drugs (LLDs) worldwide and identified possible patient and physician characteristics associated with failure to attain low-density lipoprotein cholesterol (LDL-C) goals. The aim of this analysis was to consolidate the global results from these surveys.**

***Methods*: The surveys involved patients aged ≥18 years who had been prescribed LLDs for at least 3 months without dose changes for at least 6 weeks. A single visit was scheduled for data collection, including fasting plasma lipid and glucose levels. Cardiovascular risk profile and LDL-C goal attainment were assessed according to the 2004 updated US National Cholesterol Education Program Adult Treatment Panel III guidelines.**

***Results*: In total, 35 121 patients (mean age: 60.4 years) were included, and 90.3% had been prescribed statin monotherapy. Overall, only 49.4% of patients reached their recommended LDL-C level. LDL-C goals were attained in 54.8% (5084/9273) and 22.8% (3287/14 429) of patients were at high and very high cardiovascular risk, respectively. Factors associated with an increased likelihood of LDL-C goal attainment were lower baseline cardiovascular risk; presence of diabetes mellitus, hypertension, or history of cardiovascular disease; and treatment with simvastatin, atorvastatin, or rosuvastatin (vs. all other LLDs).**

***Conclusion*: LDL-C goal attainment in patients taking LLDs is suboptimal worldwide, particularly in patients at high and very high cardiovascular risk.**

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Key words: Cardiovascular disease, Hypercholesterolaemia, Lipidlowering drugs, Low-density lipoprotein cholesterol, Undertreatment

Introduction

Cardiovascular (CV) disease is the leading cause of death globally and represents a substantial economic burden[1, 2]. Epidemiological studies have shown that elevated serum lipid and low-density lipoprotein cholesterol (LDL-C) levels, in particular, are strongly associated with an increased risk of incident CV dis-

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ease in many populations worldwide[3, 4].

Most guidelines include the reduction of LDL-C levels as a primary therapeutic target for the reduction of CV risk in both primary and secondary prevention, and they recommend LDL-C goals that are based on the CV risk category of the individual patient[5-8]. For example, the 2004 updated US National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend a therapeutic LDL-C goal of <2.6 mmol/L (100 mg/dL) for those at high CV risk, with the option to lower the goal to <1.8 mmol/L (70 mg/dL) for individuals at very high CV risk, and <3.4 mmol/L (130 mg/dL) for those at moderately high CV risk[5]. The Joint European Task Force has issued similar guidelines and recommends LDL-C levels of <1.8 mmol/L (70 mg/dL), <2.6 mmol/L (100 mg/dL), and <3.0 mmol/L (115 mg/dL) for patients at very high, high, and moderate/low CV risk, respectively[8].

Statins are the mainstay of lipid-lowering drug (LLD) therapy and have been shown to reduce both LDL-C levels and CV risk in clinical trials[9-16]. Despite the significant increase in the number of patients treated with statins and other LLDs over the past decade, surveys have shown that relatively few individuals eligible for treatment attain their recommended LDL-C level[17-19].

Aim

In order to assess the use and efficacy of LLD therapy worldwide, several Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolaemia (CEPHEUS) were conducted between 2006 and 2010. In total, 29 countries were included, and patient and physician characteristics associated with failure to attain recommended LDL-C levels were also assessed[20-28]. Here we have consolidated the global results and analyzed LLD use and LDL-C goal attainment worldwide.

Methods

Study Design and Population

Five multicentre, prospective, cross-sectional CEPHEUS studies were conducted in 29 countries across Asia (Hong Kong, Indonesia, Malaysia, Philippines, South Korea, Taiwan, Thailand, and Vietnam)[23, 26], Western Europe (Belgium, Finland, France, Greece, Ireland, Luxembourg, Netherlands, and Turkey)[22, 27, 28], Eastern Europe (Bulgaria, Poland, and Russia)[20], the Middle East (United Arab Emirates, Bahrain, Jordan, Kuwait, Oman, Qatar, and Saudi Arabia)[21, 25], and Africa (Algeria, Egypt. and South Africa)[24]. In each country, the study protocol was reviewed and approved by the Institutional Review Board and Ethics Committee governing each participating center. The surveys were performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice[29], and all participating patients provided written informed consent before enrolment.

Each survey was a single-visit study and recruitment was carried out in two stages. In the first stage, physicians with experience of treating dyslipidaemia were invited to participate. Physicians who agreed to participate were asked to complete a questionnaire about their general attitude toward the diagnosis of hypercholesterolaemia, their perception of existing guidelines, and their knowledge about available treatment options (**Supplemental Fig. 1**). In the second stage, eligible patients who attended a regular scheduled physician visit were consecutively invited to participate in the study. Patients were eligible to participate if they were ≥18 years and had been receiving LLDs for at least 3 months without dose changes for at least 6 weeks. Patients were excluded if they were found to have participated in any interventional clinical study in the preceding 90 days, were unable or unwilling to provide informed consent, or were personally involved in the conduct of the surveys. In all countries except France, before being assessed by the physician, patients also completed a questionnaire, the aim of which was to assess their personal perception of hypercholesterolaemia, their current LLD regimen, their adherence to this regimen, and their satisfaction with the treatment (**Supplemental Fig. 2**).

For each individual, physicians also completed a patient record form, which included information on the patient's demographics, current LLD therapy, and reason for initiating LLD therapy. Physicians also recorded the presence of known CV risk factors, such as smoking, diabetes mellitus, family history of premature coronary heart disease (CHD; defined as having a first-degree relative with clinical CHD or sudden death before the age of 55 years for men or 65 years for women), hypertension (defined as blood pressure ≥140/90 mmHg or current use of antihypertensive medication), any CV history, and presence of meta-

Address for correspondence: Chern-En Chiang, 201 Shih-Pai Road, Section 2, Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan
E-mail: cechiang@vghtpe.gov.tw
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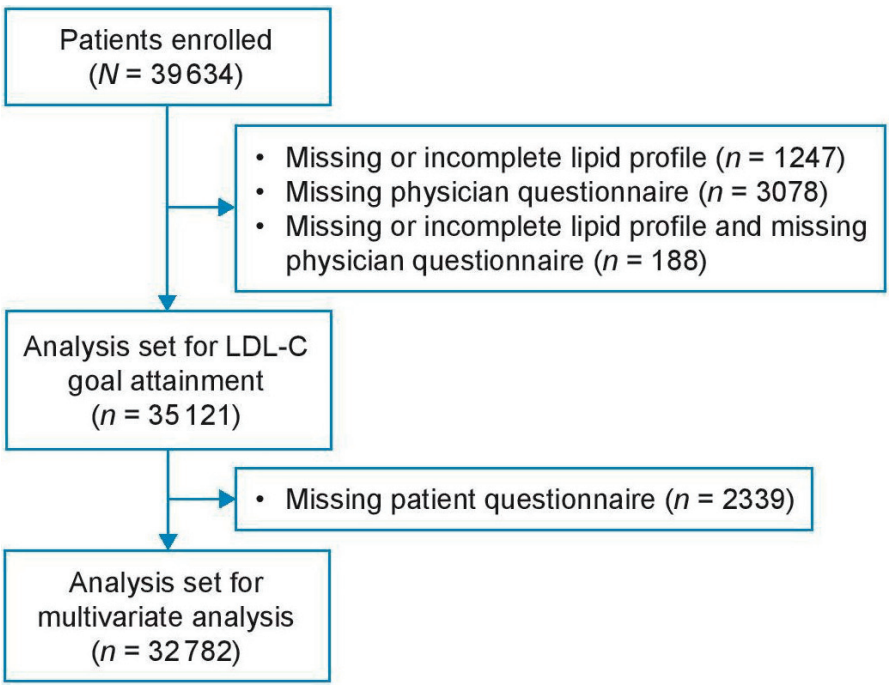

Fig. 1. Study cohort.

LDL-C goal attainment was assessed in all patients who provided their informed consent and for whom full lipid profiles and completed physician questionnaires were available. Patients who had not completed a questionnaire were excluded from the multivariate analysis.
LDL-C = low-density lipoprotein cholesterol.

bolic syndrome. Patients with metabolic syndrome were those with three or more of the following: fasting plasma triglyceride levels of at least 1.7 mmol/L (150 mg/dL), high-density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/L (40 mg/dL) for men and < 1.3 mmol/L (50 mg/dL) for women, blood pressure at least 130/85 mmHg, a fasting plasma glucose level of at least 5.6 mmol/L (100 mg/dL), and enlarged waist circumference (the definition of enlarged waist circumference varied across the regional CEPHEUS studies[20-28]; for this statistical analysis, it was defined as a waist circumference of at least 90 cm for men and at least 80 cm for women). Examination by the physician was limited to measurement of height, weight, waist circumference, and blood pressure. An overnight fasting blood sample was drawn to determine glucose and lipid (total cholesterol, HDL-C, triglycerides, and LDL-C) concentrations. Local laboratories were used at each study location for the analysis of LDL-C levels, which were either directly quantified by colorimetry or calculated using the Friedewald equation.

For the analysis of LDL-C goal attainment, the study cohort consisted of all individuals whose physician returned the physician questionnaire (answering at least one question) and for whom a current lipid profile dataset was available (i.e., valid measurements for total cholesterol, LDL-C, HDL-C, and triglycerides). In total, 35 121 patients from 29 countries were included. For the assessment of determinants of LDL-C goal attainment, patients who had not completed the patient questionnaire were excluded; therefore, the multivariate analysis included 32 782 patients from 28 countries (**Fig. 1**).

Definitions of CV Risk Categories and LDL-C Goals

The CV risk category and attainment of LDL-C goal for each patient were assessed according to the 2004 updated NCEP ATP III guidelines[5]. Patients were considered to be at very high CV risk if they had established CHD and severe and persistent CV risk factors, high CV risk if they had established CHD or CHD risk equivalents (i.e., abdominal aortic aneurysm, diabetes mellitus, peripheral vascular disease, symptomatic carotid artery disease or chronic kidney disease) or a 10-year Framingham absolute risk score > 20%[30], moderate CV risk if they had two or more CV risk factors or a 10-year Framingham absolute risk

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score between 10% and 20%[30], and low CV risk if they had no more than one CV risk factor. For patients at very high CV risk, the 2004 updated NCEP ATP III LDL-C goal was <1.8 mmol/L (70 mg/dL); for patients at high risk, the goal was <2.6 mmol/L (100 mg/dL); for patients at moderate/moderately high risk, the goal was <3.4 mmol/L (130 mg/dL); and for patients at low risk, the goal was <4.1 mmol/L (160 mg/dL).

Statistical Analysis

A two-level logistic regression model with patients at the first level and physicians as a random effect at the second level was used to determine the factors affecting attainment of LDL-C goals. In the first step, patient-related factors were screened in univariate analyses by means of a logistic model, and physician-related factors were screened in univariate analyses by means of a generalized linear mixed model (GLMM) with physician as a random effect. GLMM was carried out using the GLIMMIX procedure of the SAS system (SAS Institute, Carey, NC, USA). Following this, potential predictors were selected for inclusion in the multivariate analysis according to their statistical significance in the univariate analyses ($p<0.01$), the Bayesian information criterion, and the number of patients for whom data were available for each variable. In the second step, associations were assessed by means of a multivariate, multilevel logistic model using a backward stepwise procedure; a full model with all selected variables from the univariate analysis was constructed, and at each step, the least significant variable was removed until all parameters reached a level of significance of $p<0.01$.

Associations were assessed on the basis of the estimated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) and p values. For continuous variables, ORs were calculated for a change of one unit of the variable. Following this strategy, the final model was adjusted for the following variables: CV risk category according to the 2004 updated NCEP ATP III guidelines; country; type of LLD therapy; sex; age; presence of CVD, metabolic syndrome, hypertension, diabetes mellitus, and family history of early-onset CHD; indication for LLD therapy; smoking status; answers to the following questions: *Did your doctor give you a target cholesterol level to aim for?* (yes/no), *I am frustrated that I still do not know whether my tablets have been effective enough in lowering my cholesterol* (agree/disagree/don't know or not applicable), *I always take my tablets to lower my cholesterol every day* (agree/disagree/don't know or not applicable), *How often do you think you can miss a tablet without affecting your cholesterol levels?* (more than once a week/once a week/once every 2 weeks/once a month or less), and *In general, do you feel satisfied about the way your high cholesterol has been treated?* (yes/no) from the patient questionnaire (**Supplemental Fig. 2**); and the answer to the question *I feel frustrated that I am not always able to effectively treat my patients with CV disorders* (1, disagree strongly; 2/3/4/5, agree strongly) from the physician questionnaire (**Supplemental Fig. 1**).

Results

Patient Characteristics

Patient demographics and baseline characteristics, overall and by region, are shown in **Table 1**. The mean age of the study population was 60.4 years. The mean age was lowest in the Middle East (56.1 years) and highest in Western Europe (63.3 years). More men than women were included, both overall (men: 55.1%) and in each region (between-region range [BRR] for men: 51.2%–58.7%). The mean body mass index (BMI) was 28.4 kg/m^2, and 74.4% of patients were overweight or obese (BMI ≥25 kg/m^2). The proportion of patients who were overweight or obese was highest in the Middle East (86.3%) and lowest in Asia (54.8%). The prevalence of hypertension (blood pressure ≥140/90 mmHg or current use of antihypertensive medication) was high (72.8%, BRR: 62.8%–89.2%), and 66.3% of patients had elevated blood pressure (≥130/85 mmHg). The proportions of patients with elevated blood pressure were similar in Asia, the Middle East, and Africa (61.0%–62.1%), but were higher in Western and Eastern Europe (71.8% and 71.0%, respectively). Current smokers represented 18.0% (BRR: 13.3%–21.6%) of the study population, and 27.8% (BRR: 21.9%–32.7%) of patients had a family history of early-onset CHD. According to the 2004 updated NCEP ATP III guidelines, 41.6% of participants were at very high CV risk (BRR: 33.0%–64.0%), 35.1% at high/moderately high CV risk (BRR: 19.1%–48.4%), 11.9% at moderate CV risk (BRR: 7.9%–13.8%), and 11.4% at low CV risk (BRR: 1.1%–20.9%).

LLD Indication and Current Treatment

Overall, patients had been on LLD therapy for a mean of 3.9 years (standard deviation: 3.9 years; range: 0–47 years) (**Table 2**). Patients who were prescribed LLDs for primary CV disease prevention comprised 57.5% of the overall population (BRR: 46.2%–71.5%) and those who were prescribed LLDs for secondary CV disease prevention comprised 40.2% (BRR: 27.3%–51.7%). For the remaining patients

Table 1. Patient demographics and baseline characteristics, overall and by region

	Total (*N*=35 121)	Asia (*n*=7489)	Western Europe (*n*=12 319)	Eastern Europe (*n*=4654)	Middle East (*n*=5850)	Africa (*n*=4809)
Age (years)						
<40	1401 (4.0)	231 (3.1)	298 (2.5)	146 (3.1)	354 (6.4)	372 (7.8)
40–54	8914 (25.7)	1909 (25.5)	2231 (18.6)	985 (21.1)	2284 (39.2)	1505 (31.7)
55–69	16 285 (46.9)	3485 (46.6)	5624 (46.8)	2419 (52.0)	2487 (42.7)	2270 (47.8)
≥70	8128 (23.4)	1859 (24.8)	3860 (32.1)	1104 (23.7)	704 (12.1)	601 (12.7)
Mean ± SD	60.4 ± 11.7	61.0 ± 11.3	63.3 ± 11.2	61.4 ± 10.7	56.1 ± 11.4	56.4 ± 11.7
Sex						
Male	19 153 (55.1)	4160 (55.6)	6621 (55.0)	2377 (51.2)	3422 (58.7)	2573 (53.9)
Female	15 601 (44.9)	3328 (44.4)	5407 (45.0)	2264 (48.8)	2404 (41.3)	2198 (46.1)
BMI (kg/m^2)						
<25	8865 (25.6)	3361 (45.2)	3052 (25.5)	774 (16.7)	792 (13.7)	886 (18.6)
25–29	14 642 (42.3)	3083 (41.4)	5638 (47.1)	2099 (45.3)	2001 (34.5)	1821 (38.3)
≥30	11 093 (32.1)	995 (13.4)	3281 (27.4)	1761 (38.0)	3007 (51.8)	2049 (43.1)
Mean ± SD	28.41 ± 5.26	25.84 ± 4.07	27.91 ± 4.64	29.10 ± 4.62	31.03 ± 6.14	29.81 ± 5.74
Waist circumference (cm)						
<90 (men), <80 (women)	5577 (16.3)	2132 (28.6)	1811 (15.3)	625 (13.5)	463 (8.2)	546 (11.6)
≥90 (men), ≥80 (women)	28 680 (83.7)	5313 (71.4)	9992 (84.7)	4008 (86.5)	5209 (91.8)	4158 (88.4)
Mean ± SD	97.2 ± 13.5	90.6 ± 10.2	97.0 ± 13.2	97.2 ± 13.0	103.0 ± 13.9	101.0 ± 14.4
Blood pressure (mmHg)						
SBP/DBP <130/85	11 691 (33.7)	2913 (39.0)	3376 (28.2)	1342 (29.0)	2252 (38.6)	1808 (37.9)
SBP/DBP ≥130/85	23 002 (66.3)	4559 (61.0)	8606 (71.8)	3292 (71.0)	3585 (61.4)	2960 (62.1)
SBP mean ± SD	133.2 ± 16.7	131.8 ± 17.4	134.5 ± 15.4	134.3 ± 15.6	131.8 ± 18.1	132.6 ± 17.6
DBP mean ± SD	79.9 ± 9.8	78.9 ± 11.1	80.0 ± 8.7	82.2 ± 9.2	78.9 ± 10.2	79.9 ± 10.2
CV risk factors						
Metabolic syndrome	19 852 (58.1)	4444 (60.0)	5942 (49.4)	2753 (59.3)	3904 (67.8)	2809 (64.9)
Diabetes mellitus	13 230 (38.1)	3286 (44.2)	2749 (22.9)	1179 (22.9)	3631 (62.2)	2385 (50.0)
Hypertension*	25 304 (72.8)	6305 (84.2)	7544 (62.8)	4151 (89.2)	3861 (66.2)	3443 (72.2)
Smoking†	6245 (18.0)	1617 (21.6)	2216 (18.4)	860 (18.5)	918 (15.7)	634 (13.3)
Family history of early-onset CHD‡	9642 (27.8)	2120 (28.3)	3450 (28.8)	1523 (32.7)	1277 (21.9)	1272 (26.7)
Age§	28 858 (83.1)	6423 (85.8)	10 689 (89.0)	4031 (86.7)	4224 (72.5)	3491 (73.5)
CV disease history						
CHD	13 639 (39.3)	3547 (47.6)	3499 (29.1)	2789 (59.9)	1923 (32.9)	1881 (39.4)
Peripheral arterial disease	2401 (6.9)	306 (4.1)	1168 (9.7)	483 (10.4)	165 (2.8)	279 (5.8)
Carotid artery disease	407 (5.5)	407 (5.5)	NA	NA	NA	NA
Abdominal aortic aneurysm	56 (0.8)	56 (0.8)	NA	NA	NA	NA
ACVD	2229 (8.5)	NA	990 (8.3)	837 (18.0)	204 (3.5)	198 (5.5)
Ischaemic stroke	65 (5.6)	NA	NA	NA	NA	65 (5.6)
CV risk category¶						
Very high	14 429 (41.6)	3664 (49.0)	3960 (33.0)	2973 (64.2)	1929 (33.1)	1903 (39.9)
High	9273 (26.7)	2151 (28.8)	2353 (19.6)	536 (11.6)	2586 (44.3)	1647 (34.6)
Moderately high	2904 (8.4)	560 (7.5)	1514 (12.6)	349 (7.5)	239 (4.1)	242 (5.1)
Moderate	4142 (11.9)	1018 (13.6)	1655 (13.8)	554 (12.0)	463 (7.9)	452 (9.5)
Low	3954 (11.4)	86 (1.1)	2511 (20.9)	221 (4.8)	616 (10.6)	520 (10.9)

ACVD=atherosclerotic cerebrovascular disease; BMI=body mass index; CHD=coronary heart disease; CV=cardiovascular; DBP=diastolic blood pressure; NA=not available (data not collected); NCEP ATP III=US National Cholesterol Educational Program Adult Treatment Panel III; SBP=systolic blood pressure; SD=standard deviation.
Numbers are *n* (%) unless otherwise stated and are based on patients with non-missing data.
* Blood pressure ≥140/90 mmHg or on antihypertensive medication.
† Any smoking in the past month.
‡ First-degree relative(s) with clinical coronary heart disease or sudden death at age <55 years for men and <65 years for women.
§ Age ≥45 years for men and ≥55 years for women.
¶ As defined by the 2004 updated NCEP ATP III guidelines[5].

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Table 2. Lipid-lowering drug treatment, overall and by region

	Total (n=35 121)	Asia (n=7489)	Western Europe (n=12 319)	Eastern Europe (n=4654)	Middle East (n=5850)	Africa (n=4809)
Current treatment						
Statin monotherapy	31 299 (90.3)	6371 (85.1)	10 650 (89.1)	4344 (93.8)	5479 (93.8)	4455 (93.8)
Atorvastatin	10 775 (32.9)	1863 (27.4)	3260 (28.6)	1516 (34.1)	2445 (44.1)	1691 (37.2)
Fluvastatin	900 (2.8)	154 (2.3)	400 (3.5)	47 (1.1)	74 (1.3)	225 (5.0)
Lovastatin	226 (0.7)	84 (1.2)	46 (0.4)	85 (1.9)	7 (0.1)	4 (0.1)
Pitavastatin	145 (0.4)	145 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pravastatin	1533 (4.7)	165 (2.4)	1164 (10.2)	90 (2.0)	51 (0.9)	63 (1.4)
Rosuvastatin	6614 (20.2)	1807 (26.6)	2462 (21.6)	1083 (24.4)	705 (12.7)	557 (12.3)
Simvastatin	11 106 (33.9)	2153 (31.7)	3318 (29.1)	1523 (34.3)	2197 (39.7)	1915 (42.2)
Fibrate monotherapy	1291 (3.7)	404 (5.4)	658 (5.5)	98 (2.1)	54 (0.9)	77 (1.6)
Other monotherapy	130 (0.4)	23 (0.3)	90 (0.8)	3 (0.1)	5 (0.1)	9 (0.2)
Combination therapy*	1941 (5.6)	687 (9.2)	559 (4.7)	187 (4.0)	302 (5.2)	206 (4.3)
Reason for treatment						
Primary prevention	19 478 (57.5)	3490 (47.7)	7872 (66.2)	2159 (46.6)	3752 (71.5)	2205 (46.2)
Secondary prevention**	13 631 (40.2)	3714 (50.7)	3690 (31.0)	2395 (51.7)	1435 (27.3)	2397 (50.3)
Familial hypercholesterolaemia	763 (2.3)	116 (1.6)	336 (2.8)	81 (1.7)	62 (1.2)	168 (3.5)
Duration of treatment (years)						
Mean ± SD	3.9 ± 3.9	2.9 ± 3.0	4.9 ± 4.5	3.1 ± 3.3	3.7 ± 3.4	3.1 ± 2.9

SD=standard deviation.
Numbers are n (%) unless otherwise stated and are based on patients with non-missing data.
*Combination therapy was simvastatin plus ezetimibe
**Includes patients whose reason for treatment was diabetes mellitus.

(2.3%, BRR: 1.2%−3.5%), the reason for LLD treatment was a history of familial hypercholesterolaemia. Statin monotherapy was the most commonly prescribed LLD therapy (90.3%). Within regions, the proportions of patients on statin monotherapy were greater than 90%, with the exception of Asia (85.1%) and Western Europe (89.1%). Simvastatin was the most commonly used statin monotherapy, being prescribed to 33.9% of all patients receiving statin monotherapy, followed by atorvastatin (32.9%) and rosuvastatin (20.2%).

LDL-C Goal Attainment

Fig. 2 shows the proportions of patients attaining their 2004 updated NCEP ATP III LDLC goal according to sex, overall and by region. In total, 49.4% of patients attained their LDLC goal. The proportions of patients attaining their recommended LDL-C goal were higher than the overall proportion in Africa, Western Europe, and the Middle East (57.9%, 56.6%, and 52.4%, respectively). Poor control of LDL-C levels was most apparent in Eastern Europe, where only 26.0% of individuals had attained their desired LDL-C level. Overall and across all regions, the proportions of patients who attained their LDL-C goal were higher for women than for men (51.9% vs. 47.4%).

Attainment of LDL-C goal varied according to the CV risk category (**Fig. 3**); 89.8% (BRR: 79.1%−91.1%) of individuals at low CV risk attained their LDL-C goal compared with only 54.8% (BRR: 34.1%−65.7%) and 22.8% (BRR: 9.8%−36.9%) of patients in the high and very high CV risk categories, respectively.

The type of LLD therapy also had an impact on the proportions of patients attaining their LDL-C goal (**Fig. 4**). Overall, the highest proportion of patients attaining their LDL-C goal was observed for those who were prescribed statin monotherapy (49.7%), followed by those who were prescribed any combination therapy (46.9%) and fibrate monotherapy (46.0%). The proportion of patients attaining their LDL-C goal was lowest in those who received any other monotherapy (33.1%), although it should be noted that this group included only 130 individuals.

Determinants of LDL-C Goal Attainment

The factors significantly affecting LDL-C goal attainment in the multivariate adjusted model are summarized in **Fig. 5**. In this model, women were less

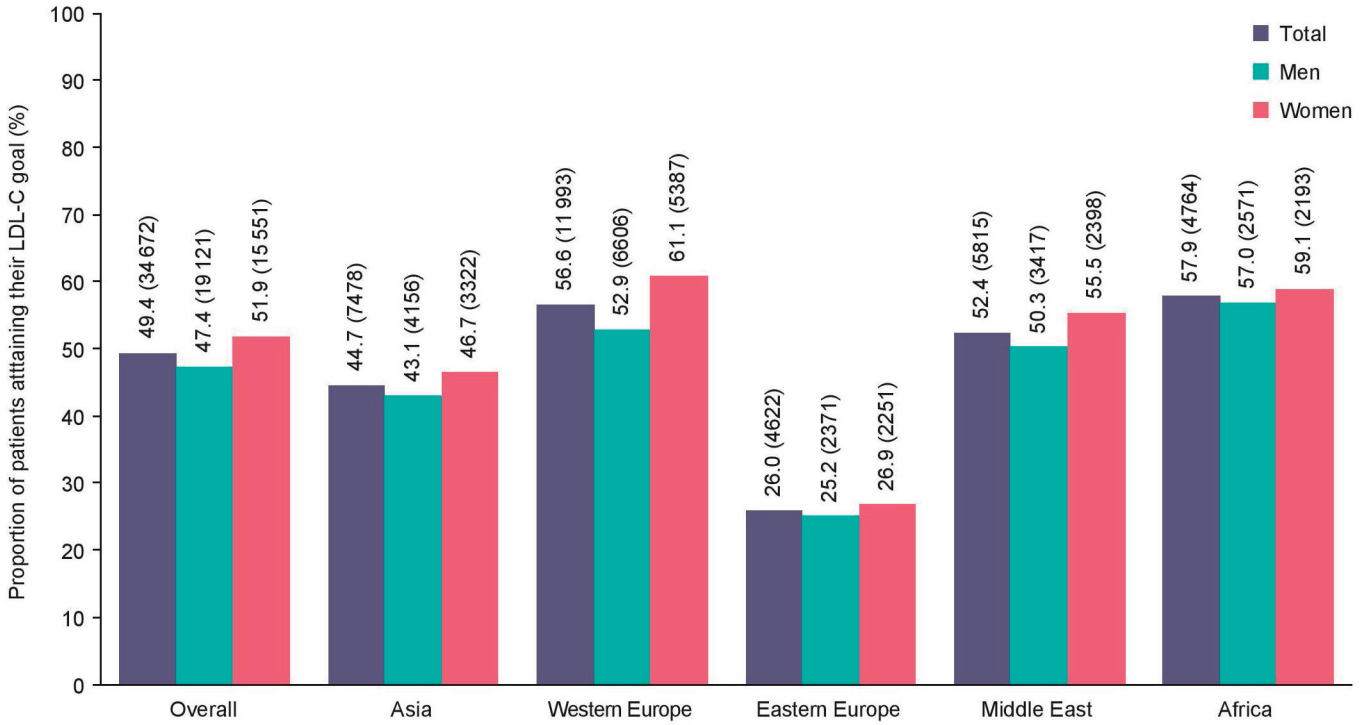

Fig. 2. Proportions of patients attaining their LDL-C goal according to sex, overall and by region.

LDL-C goal attainment was assessed according to the 2004 updated US National Cholesterol Education Program Adult Treatment Panel III guidelines[5]. Numbers in brackets indicate the total number of patients in each category.
LDL-C = low-density lipoprotein cholesterol.

likely to attain their LDL-C goal than men (OR: 0.71; 95% CI: 0.65−0.77). Higher age was associated with better odds of attaining LDL-C goal (OR: 1.01; 95% CI: 1.01−1.02 for a 1-year increase in age). Presence of diabetes mellitus, hypertension, or a history of CV disease was associated with a significant increase in the proportion of patients attaining their recommended LDL-C level. In contrast, current smokers and individuals with metabolic syndrome or a family history of early-onset CHD were less likely to attain their recommended LDL-C level than those without such CV risk factors (**Fig. 5**).

The likelihood of attaining their LDL-C goal was greater in patients who had been given a LDL-C goal by their physician than in those who had not [answer to the following question: *Did your doctor give you a target cholesterol level to aim for?* (yes/no) from the patient questionnaire]. Similarly, those who were satisfied with their treatment were more likely to attain their LDL-C goal than those who were not [answer to the following question: *In general, do you feel satisfied about the way your high cholesterol has been treated?* (yes/no) from the patient questionnaire]. Patient-reported adherence to LLD therapy and perceived importance of adherence were found to be significantly associated with LDL-C goal attainment [answers to the following questions: *I always take my tablets to lower my cholesterol every day* (agree/disagree/don't know or not applicable) and *How often do you think you can miss a tablet without affecting your cholesterol levels?* (more than once a week/once a week/once every 2 weeks/once a month or less) from the patient questionnaire] (**Fig. 5**).

Patients who were prescribed simvastatin, atorvastatin, or rosuvastatin were more likely to attain their recommended LDL-C level than those who were prescribed any other LLD therapy. Rosuvastatin was associated with the greatest likelihood of LDL-C goal attainment relative to any other LLD therapy (OR: 1.81; 95% CI: 1.59−2.06). The lower their CV risk, the more likely patients were to attain their LDL-C goal; individuals in the low and moderate CV risk categories were much more likely to attain their LDL-C goal than those in the very high CV risk category (OR: 235.48; 95% CI: 167.64−330.78 and OR: 85.14; 95% CI: 63.11−114.86, respectively). Of the indications for LLD therapy that were assessed (primary prevention, secondary prevention, and familial

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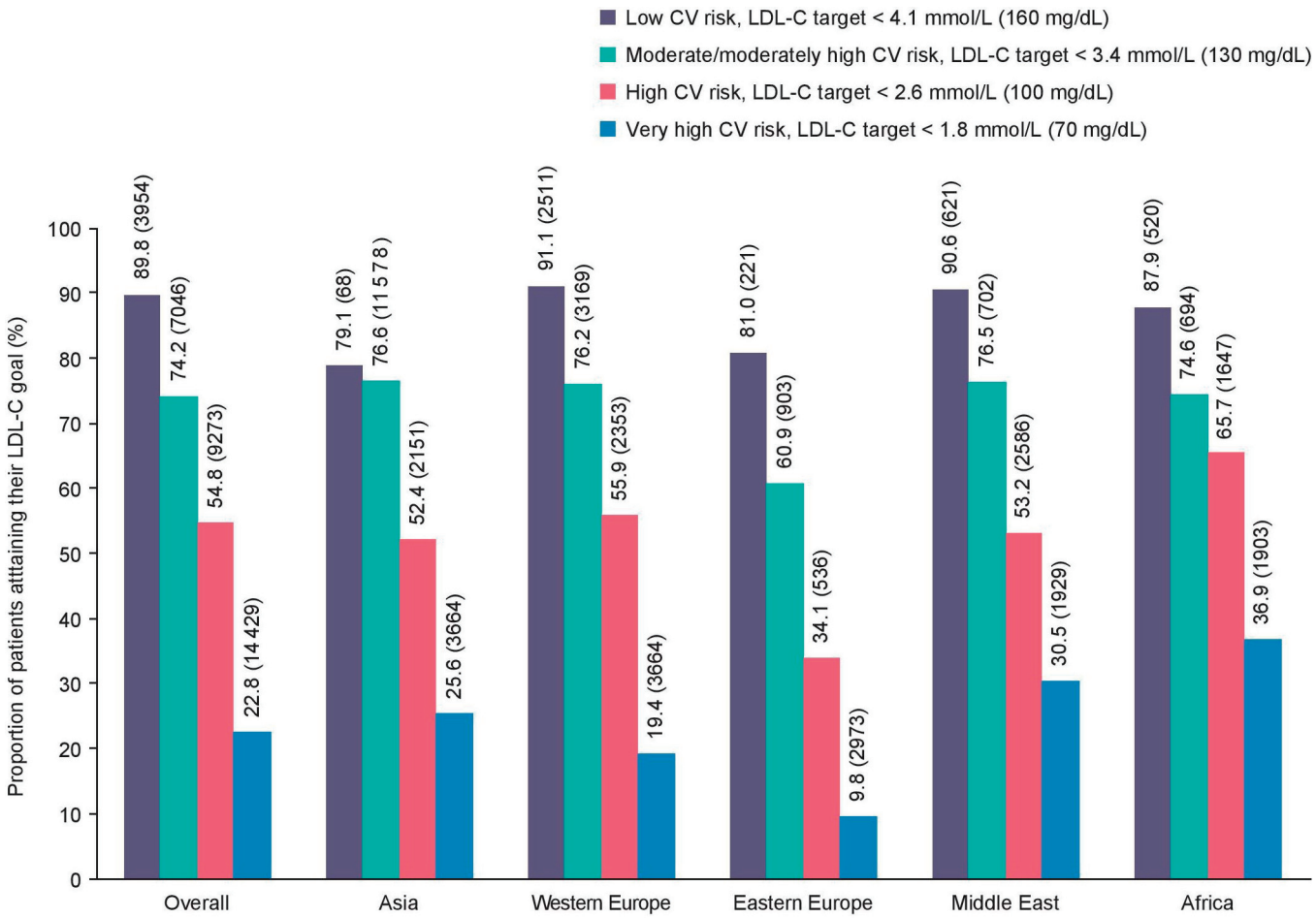

Fig. 3. Proportions of patients attaining their LDL-C goal according to CV risk, overall and by region.

CV risk profile and LDL-C goal attainment were assessed according to the 2004 updated US National Cholesterol Education Program Adult Treatment Panel III guidelines[5]. Numbers in brackets indicate the total number of patients in each category.
CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol.

hypercholesterolaemia) only secondary prevention was found to be associated with LDL-C goal attainment (OR: 1.24; 95% CI: 1.09−1.40).

Discussion

The combined results from CEPHEUS observational studies conducted in 29 countries across five regions highlight that LDL-C goal attainment in patients prescribed LLDs is poor worldwide. At the time of the surveys, <50% of patients attained their LDL-C goal despite having been on LLD therapy for a mean of 3.9 years. Lipid level control was good in patients at low CV risk, with approximately 90% of such patients attaining their recommended LDL-C level. In contrast, goal attainment was much lower in high and very high CV risk patients, with only approximately 55% and 23% of these patients having adequately controlled LDL-C levels, respectively.

This meta-analysis provides a global overview of hypercholesterolaemia treatment for the period when the studies were conducted (2006−2010) based on a large number of patients of different ethnic origins. However, it has some limitations. The surveys were conducted in the same way in the different countries, but there may be considerable variability in clinical practice and reimbursement between regions, countries, and study sites. Moreover, only willing patients and physicians (selected based on having experience of treating dyslipidaemia) were included in the study cohort and it may therefore not be representative of general clinical practice, although these sources of bias would, if anything, lead to an overestimation of the proportion of patients attaining LDL-C goals. It

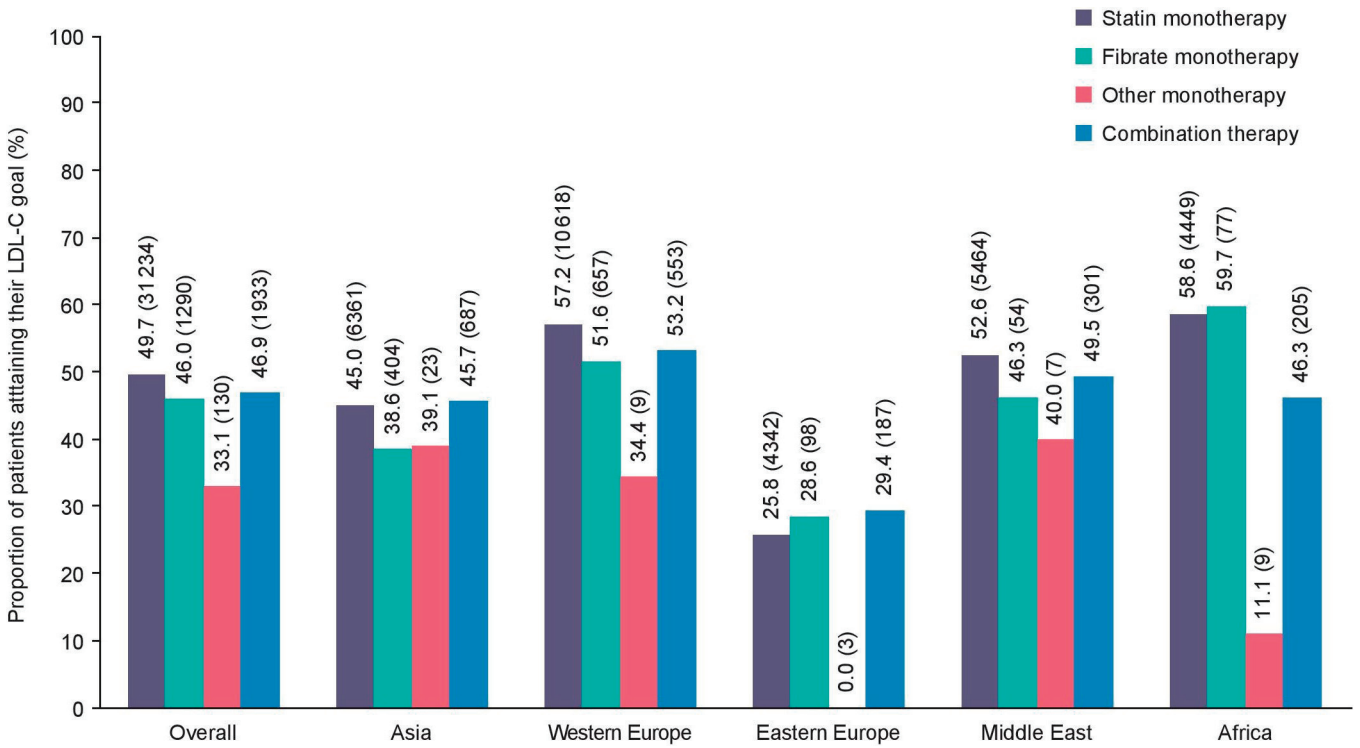

Fig. 4. Proportions of patients attaining their LDL-C goal according to lipid-lowering therapy, overall and by region.

LDL-C goal attainment was assessed according to the 2004 updated US National Cholesterol Education Program Adult Treatment Panel III guidelines[5]. Numbers in brackets indicate the total number of patients in each category.
LDL-C = low-density lipoprotein cholesterol.

should also be noted that the patient and physician questionnaires were not validated but used for exploratory purposes only. Finally, the surveys collected a limited amount of data. For example, data on dietary and other lifestyle interventions, adverse events, differences in healthcare policies, out-of-pocket costs, and patients' socioeconomic status and level of education were not recorded. These factors may be determinants of LDL-C goal attainment and are, therefore, potential confounders in this study.

The results of the present study are in line with those reported by other studies worldwide. For example, in the third European Action on Secondary Prevention to Reduce Events (EUROASPIRE III) survey, 57.3% of patients on LLDs were found to have attained their LDL-C goal[18]. The CEPHEUS results are also in line with those from the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study, in which only 48% of 2622 patients with hypercholesterolaemia and newly initiated on statin monotherapy attained their NCEP ATP III goal for LDL-C after 12 months[17]. However, the Lipid Treatment Assessment Project 2 (L-TAP2) study[19], reported a higher rate of LDL-C goal attainment than the combined CEPHEUS studies. The L-TAP2 study was conducted in nine countries across Europe (France, Netherlands, and Spain), the Americas (USA, Canada, Brazil, and Mexico) and Asia (South Korea and Taiwan), and 73% of 9955 evaluated patients were shown to have attained their LDL-C goal. Although LLD therapy distributions were similar in both studies, it should be noted that there were more patients at low and moderate CV risk in the L-TAP2 study than in the CEPHEUS surveys (40.4% vs. 23.3%). Both studies reported better goal attainment in the low and moderate CV risk categories than in the higher CV risk category. Better LDL-C goal attainment was also observed for Japanese patients with low and moderate CV risk compared with those with a high CV risk in the large (N=22 121) Japan Lipid Assessment Program (J-LAP) study[31]. Overall, LDL-C goal attainment was substantially higher in the J-LAP study than in the CEPHEUS study (63.7% vs. 49.4%). As with the L-TAP2 study, this may be because of the higher proportion of patients with low and moderate CV risk that were included compared with CEPHEUS (55.7%

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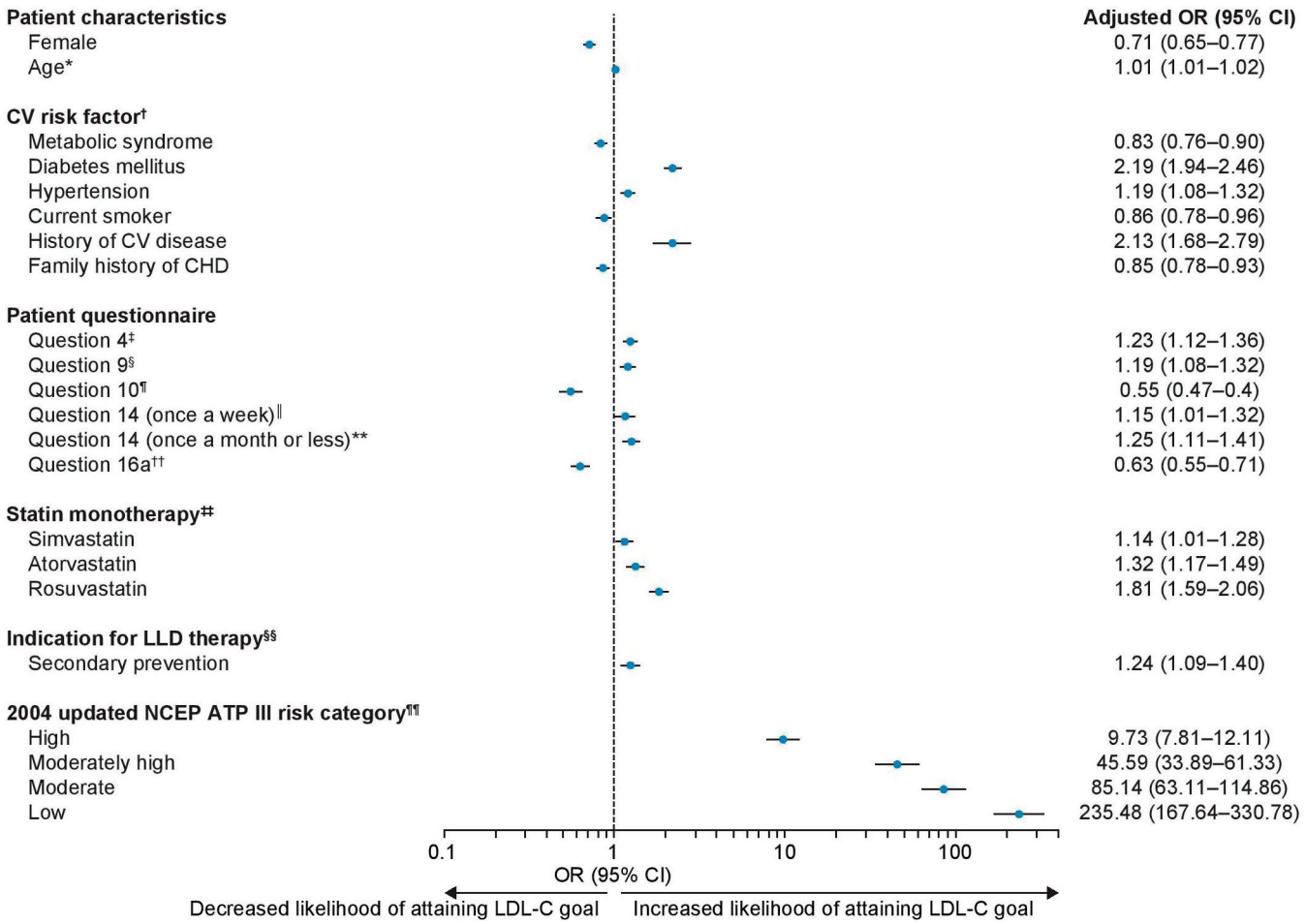

Fig. 5. Determinants of LDL-C goal attainment based on 32 782 patients from 28 countries.

LDL-C goal attainment was assessed according to the 2004 updated US National Cholesterol Education Program Adult Treatment Panel III guidelines[5].

*Continuous variable (OR calculated for an increase of 1 year).

†Relative to absence of CV risk factor.

‡Question 4: Did your doctor give you a target cholesterol level to aim for? (no/yes).

§Question 9: I am frustrated that I still do not know whether my tablets have been effective enough in lowering my cholesterol. (disagree/ agree).

¶Question 10: I always take my tablets to lower my cholesterol every day. (disagree/ agree).

‖Question 14: How often do you think you can miss a tablet without affecting your cholesterol levels? (once a week/more than once a week).

**Question 14: How often do you think you can miss a tablet without affecting your cholesterol levels? (once a month or less/more than once a week).

††Question 16a: In general, do you feel satisfied about the way your high cholesterol has been treated? (no/yes).

‡‡Relative to all other therapies.

§§Relative to all other indications.

¶¶Relative to very high CV risk.

CI=confidence interval; CHD=coronary heart disease; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; LLD=lipid-lowering drug; NCEP ATP III=US National Cholesterol Educational Program Adult Treatment Panel III; OR=odds ratio.

vs. 23.3%). However, LDL-C goal attainment was not as high in the J-LAP study as it was in the L-TAP2 study (63.7% vs. 73%), despite the higher proportion of low and moderate CV risk patients included in the former (55.7% vs. 40.4%). These studies were similar in terms of the distribution of LLD therapy, with the exception that no patients in the J-LAP study were taking rosuvastatin compared with 12% of patients in the L-TAP2 study. This factor, among others, may have contributed to the higher rate of LDL-C goal

attainment in J-LAP vs. L-TAP2 because rosuvastatin has been shown to be more effective than at least one other statin (atorvastatin) for LDL-C goal attainment in Japanese patients[32].

There are several potential explanations for the overall poor attainment of LDL-C goals observed in the CEPHEUS studies. Although 92.4% of physicians in these studies reported that they used clinical practice guidelines, particularly NCEP ATP III (used by 50.7%), to set an individual patient's treatment goal, only 71.2% of patients indicated they had been given a cholesterol goal. Given the positive association observed between patients' awareness of their recommended LDL-C level and attainment of that goal, more efforts are required from physicians to ensure that their patients are well informed about their treatment goal. Similarly, there is room for improvement in patient education and information because only 71.7% of patients reported having heard or been told about LDL-C and 37.9% did not know whether they had attained their recommended cholesterol level.

Another contributor to the low rate of goal attainment may be the fact that only a few patients were prescribed high-intensity statin therapy[33]. Although 68.3% of individuals were at high or very high CV risk, only 5.3% and 3.5% of patients on LLD monotherapy were prescribed doses of atorvastatin of at least 40 mg/day or doses of rosuvastatin of at least 20 mg/day, respectively. Most patients were on low- or medium-intensity statins, and the majority (63.2%) of the patients were still on the same LLD regimen as first prescribed. Drug dose had been increased for only 8.7% of patients since their first LLD prescription. Reasons for this conservative therapeutic approach are not clear, but may reflect patients' or physicians' concerns about possible higher risks of adverse events with higher doses of LLDs. Moreover, physicians may be reluctant to increase drug dosage if they think that failure to attain recommended cholesterol goals is partly because of poor patient adherence and/or failure to implement recommended lifestyle changes. Other determinants of this clinical inertia may include disagreement with or insufficient knowledge of the current guidelines.

Although patient non-adherence to treatment could be a factor in the low rate of LDL-C goal attainment, adherence was not assessed by tablet counts or prescription records in the CEPHEUS studies. However, 35.3% of patients reported that they sometimes forgot to take their cholesterol-lowering tablets, and 49.4% admitted forgetting to take their tablets once every 2 weeks or more often. This suboptimal adherence to LLD therapy is in line with results from many studies worldwide and has been shown to be associated with increased CV morbidity and mortality[34].

Among the potential factors studied to identify the determinants of LDL-C goal attainment, increasing age was associated with better LDL-C control. The reason for this is unclear, but it should be noted that allocation of statin therapy (relative to any other LLD therapy) was higher in patients aged 55 years or older than in those aged 18−39 years. Statins have been shown to be more efficacious than other current LLDs to lower LDL-C levels[8], and this may explain, at least in part, the decreased likelihood of younger patients attaining their LDL-C goal compared with older individuals.

This study also highlighted a difference between men and women. Although the proportions of patients who attained their LDL-C goal were greater in women than in men overall (51.9% vs. 47.4%), the multivariate adjusted analysis revealed that women were less likely than men to attain their goal. The reason for this difference is unclear, but a similar finding has been reported in several studies[35-39]. For example, in the NCEP Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II, the adjusted OR for LDL-C goal attainment was 0.76 (95% CI: 0.62−0.93) for women compared with men with CHD or CHD risk equivalents[35]. A similar sex disparity was observed in a Chinese study, with an adjusted OR of 0.77 (95% CI: 0.60−0.90) for women relative to men in patients at high or very high CV risk[36]. Although differences in treatment between men and women have been suggested to explain this disparity[37-39], further research is required to understand and address this phenomenon.

Familial hypercholesterolaemia was not associated with a significant reduction in the prevalence of LDL-C goal attainment, with a similar rate observed compared with the overall study population (49.5% vs. 50.4%). This is despite familial hypercholesterolaemia typically being less responsive to cholesterol lowering methods. It may be that clinicians tend to treat patients with familial hypercholesterolaemia more aggressively, thus compensating for higher treatment resistance. Alternatively, patients with familial hypercholesterolaemia may be more adherent. Indeed, the provision of genetic test information (required for the diagnosis of familial hypercholesterolaemia) has previously been shown to significantly improve adherence to LLDs[40, 41]. Further investigation of this patient sub-group may be warranted.

The three most common statin monotherapies used in the CEPHEUS studies (simvastatin, atorvastatin, and rosuvastatin) were associated with an increased likelihood of LDL-C goal attainment, rela-

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tive to all other LLDs. This is in line with the established superiority of statins compared with other LLDs in lowering LDL-C levels[8] and is reflected in the higher overall goal attainment with statins than with other LLDs. The highest likelihood of LDL-C goal attainment was observed with rosuvastatin and is in keeping with the superiority of rosuvastatin in lowering LDL-C compared with other statins[42, 43].

After the CEPHEUS studies had been conducted, the American Heart Association and American College of Cardiology published new guidelines for the prevention of CV disease and the management of dyslipidaemia[33]. These guidelines define specific groups of patients who should be prescribed either moderate- or high-intensity statin therapy without aiming for a predefined LDL-C goal. This approach identifies four statin benefit groups in an attempt to simplify the management of CV disease prevention. However, LDL-C goals as recommended by the current European guidelines[8] remain important because they may be a motivational tool for patients to implement lifestyle and dietary changes and to adhere to their treatment. In addition, LDL-C goals provide guidance to physicians when making personalized treatment decisions according to a patient's CV profile and they allow quantitative benchmarking to be carried out.

In conclusion, the results of this survey highlight the suboptimal management of hypercholesterolaemia worldwide, particularly in patients at high and very high CV risk. Attaining LDL-C goals set by the stringent guidelines will require a more aggressive approach, which may include better adherence to guidelines, enhanced patient and physician education, novel strategies to improve patient adherence to treatment, and development of more efficacious LLDs for statin-intolerant patients. Clinical inertia should also be addressed to ensure that LLDs in general, and the most effective statins in particular, are used and up-titrated as recommended by the guidelines.

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Conflicts of Interest

C.-E.C. has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Tanabe, Takeda and TTY Biopharm and has served on advisory boards for AstraZeneca and Merck Sharp & Dohme. J.F. has received honoraria from Amgen, AstraZeneca, Merck Sharp & Dohme, Sanofi-Aventis and Servier. F.J.R. has received research grants from Amgen and Regeneron/Sanofi-Aventis and honoraria from Amgen, AstraZeneca and Regeneron/Sanofi-Aventis and has served on advisory boards for Amgen, AstraZeneca and Regeneron/Sanofi-Aventis. J.S. has received research grants from Kuhnil Pharmaceutical, Genzyme and Otsuka Pharmaceutical. K.M.H. is an employee of AstraZeneca. M.P.H. has received honoraria from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, LifeScan, Menarini, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis and Takeda and has served on advisory boards for Abbott, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis and Takeda. N.N.G. and A.S. have no conflicts of interest to disclose.

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Supplemental Fig. 1.
Questionnaire used to assess physicians' general attitudes toward the diagnosis of hypercholesterolemia, their perception of existing guidelines, and their knowledge about available treatment options

Q1 For what proportion of patients do you set individual target cholesterol levels expressed as an actual number?

_____%

Q2 Which lab measures do you generally use to set individual target cholesterol levels?

You can give more than one answer.

☐ Total cholesterol ☐ HDL-C

☐ LDL-C ☐ Triglycerides

Q3 Do you utilize any guidelines to help to establish individual cholesterol targets for your patients?

☐ Yes ☐ No

➲ CONTINUE ➲ GO TO Q5

Q4 a) Which guidelines do you use?

You can give more than one answer.

If you use more than one guideline, please answer the following question.

b) Which **one** do you mainly use?

Please select one answer only.

	Use	**Mainly use**
Joint European guidelines (SCORE)	☐	☐
NCEP ATP III guidelines (FRAMINGHAM)	☐	☐
National guidelines	☐	☐
Local healthcare authority guidelines/recommendations	☐	☐
Individual practice guidelines/recommendations	☐	☐
Other (write in) _____	☐	☐
Unable to name the precise guidelines used	☐	☐

Q5 When patients are first diagnosed with hypercholesterolaemia, do you generally inform them of their cholesterol level?

☐ Yes ☐ No

Advance Publication
Journal of Atherosclerosis and Thrombosis
Accepted for publication: September 25, 2015
Published online: December 2, 2015

Q6 In what proportions of patients do you:

a) not mention extent of reduction at all _____%

b) provide a target cholesterol level expressed as an actual number _____%

c) provide a percentage or proportion reduction _____%

d) provide a more general description such as need to reduce by 'a little' or 'a lot' _____%

a+b+c+d must add up to 100%

Q7 When informing your patients, which of the following types of lipid parameters measurement do you generally use?

You can give more than one answer.

☐ Total cholesterol ☐ HDL-C

☐ LDL-C ☐ Triglycerides

Q8 Focussing now on **pharmacological treatment** for hypercholesterolaemia, for what percentage of your patients do you recommend treatment with:

a) statins _____%

b) fibrates _____%

c) bile acid sequestrants _____%

d) other _____%

a+b+c+d must add up to 100%

Q9 How frequently do you see the patient to review their cholesterol level?

☐ Do not review

☐ Less frequently than once per year

☐ Once per year

☐ Once every 6 months

☐ Once every 3 months

☐ More frequently than once every 3 months

Please circle the most applicable number that meets how much you agree/disagree with each one (1 is disagree strongly and 5 is agree strongly).
The same scale will be used for all statements.

		Disagree strongly				Agree strongly
	General					
Q10	I feel frustrated that I am not always able to effectively treat my patients with cardiovascular disorders	1	2	3	4	5
	Guidelines and goal					
Q11	I find it stressful trying to get my patients to their cholesterol targets	1	2	3	4	5
Q12	I feel pressured to get patients to their target cholesterol level	1	2	3	4	5
Q13	A sufficient number of patients reach their target cholesterol levels	1	2	3	4	5
Q14	I'm frustrated that the guidelines instruct me to advise lifestyle changes alone as first-line therapy in all patients	1	2	3	4	5
Q15	I'm frustrated that the guidelines instruct me to prescribe a low dose of lipid-lowering drug to all patients and titrate upwards	1	2	3	4	5
	Pharmacological treatment					
Q16	I tend to prescribe a lipid-lowering drug only to patients who have proved they can adhere to diet and exercise change	1	2	3	4	5
Q17	Patient compliance decreases if lipid-lowering drugs take too long to have an effect	1	2	3	4	5
Q18	I feel constrained to use less-effective lipid-lowering drugs first line	1	2	3	4	5
Q19	Patients become concerned that their condition is more severe if their lipid-lowering drug is titrated up	1	2	3	4	5

Advance Publication
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Q20	Patients become concerned that their condition is more severe if their lipid-lowering drug is frequently changed	1	2	3	4	5	

Q21 In summary, thinking of all your hypercholesterolaemia patients, what percentage of those that have been set a target cholesterol level fall into the following categories?

a) Reached their target cholesterol level and continue to stay at this level _____%

b) Generally stay at their target cholesterol level but their cholesterol is sometimes too high _____%

c) Reached their target cholesterol level in the past but have now relapsed _____%

d) Have never reached their target cholesterol level _____%

a+b+c+d must add up to 100%

☐ Never set target cholesterol levels

Q22 In general, once a patient has reached their target cholesterol level, after what length of time do you ask that patient to come back to review their hypercholesterolaemia?

_____ months

☐ Never set target cholesterol levels

Q23 What percentage of patients actually attends this review?

_____%

Supplemental Fig. 2.
Questionnaire used to assess patients' personal perceptions of hypercholesterolemia, their current lipid-lowering drug regimen, their adherence to this regimen, and their satisfaction with the treatment

Q1	Have you heard of or been told about bad cholesterol, otherwise known as LDL-C? ☐ Yes ☐ No ☐ Don't know/Can't remember
Q2	Have you ever heard of or been told about good cholesterol, otherwise known as HDL-C? ☐ Yes ☐ No ☐ Don't know/Can't remember
Q3	When you were first told by your doctor that you had high cholesterol, did your doctor tell you what your cholesterol level was? ☐ Yes ☐ No ➲ CONTNUE ➲ GO TO Q5
Q4	Did your doctor give you a target cholesterol level to aim for? ☐ Yes ☐ No
Q5	As a first step when you were diagnosed with high cholesterol, did the doctor: *Please select one answer only.* ☐ **only** advise you to change your lifestyle e.g. change your diet, stop smoking and/or do more exercise? ☐ **only** prescribe a tablet? ☐ **both** advise lifestyle changes and prescribe a tablet? ☐ **neither** advise lifestyle changes nor prescribe a tablet?
Q6	Which **one** of the following best describes the number of times your cholesterol-lowering tablet has been changed since it was first prescribed? ☐ Still on the same tablet ➲ GO TO Q8 ☐ Still on the same tablet but the dose has increased ➲ CONTINUE ☐ Have changed tablets once or twice (may include adding another tablet) ➲ CONTINUE ☐ Have changed tablets several times (may also include adding other tablets) ➲ CONTINUE

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Q7 **If Q6 = b, c or d**

How did you feel about your cholesterol-lowering tablets having to be changed i.e. having the dose of your tablet increased or taking a different tablet? Please answer Yes or No to the following.

	Yes	No
a) Satisfied	☐	☐
b) Concerned that your condition was now a 'serious illness'	☐	☐
c) No strong feelings	☐	☐
d) Less motivated to keep taking tablets	☐	☐
e) Irritated at having to keep making changes	☐	☐
f) Disappointed that treatment was not successful	☐	☐

Q8 I am satisfied with the level of information available to me about high cholesterol.

☐ Agree ☐ Disagree ☐ Don't know/Not applicable

Q9 I am frustrated that I still do not know whether my tablets have been effective enough in lowering my cholesterol.

☐ Agree ☐ Disagree ☐ Don't know/Not applicable

Q10 I always take my tablets to lower my cholesterol every day.

☐ Agree ☐ Disagree ☐ Don't know/Not applicable

Q11 I stopped taking my tablets when my cholesterol level returned to normal.

☐ Agree ☐ Disagree ☐ Don't know/Not applicable

Q12 Sometimes I forget to take my cholesterol-lowering tablets.

☐ Agree ☐ Disagree ☐ Don't know/Not applicable

➲ CONTINUE ➲ GO TO Q14 ➲ GO TO Q14

Q13 Approximately how often do you forget to take your cholesterol-lowering tablets? Please select the option which most closely applies to you.

☐ More than once a week ☐ Once a week

☐ Once every 2 weeks ☐ Once a month or less

Q14 How often do you think you can miss a tablet without affecting your cholesterol levels?

☐ More than once a week ☐ Once a week

☐ Once every 2 weeks ☐ Once a month or less

Q15 Which of the following best describes your current situation?

☐ I have not been given a target cholesterol level

☐ I have not reached my target cholesterol level

☐ I'm not sure whether I have reached my target cholesterol level

☐ I have reached my target cholesterol level

Q16 In general, how do you feel about the way your high cholesterol has been treated?

Please answer Yes or No to the following.

	Yes	No
a) Satisfied	☐	☐
b) Motivated	☐	☐
c) Concerned	☐	☐
d) Frustrated	☐	☐
e) Disappointed	☐	☐
f) Confused	☐	☐
g) No strong feelings	☐	☐

Q17 In general, how often do you see your doctor for a check-up of your cholesterol level?

☐ More frequently than once every 3 months

☐ Every 3 months

☐ Every 6 months

☐ Every year

☐ Less often than once a year

☐ Do not have check-ups

☐ Don't know/Can't remember