Original Article

Prevalence and Control of Hypercholesterolaemia as Defined by NCEP-ATPIII Guidelines and Predictors of LDL-C Goal Attainment in a Multi-Ethnic Asian Population

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Abstract

Introduction: Few studies in Asia have assessed the burden of hypercholesterolaemia based on the global cardiovascular risk assessment. This study determines the burden of hypercholesterolaemia in an Asian population based on the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) guidelines, and examines predictors of low-density lipoprotein cholestrol (LDL-C) goal attainment. Materials and Methods: Five thousand and eighty-three Chinese, Malays and Asian-Indians living in Singapore were assigned to coronary heart disease (CHD)-risk category based on the NCEP-ATPIII guidelines. Awareness, treatment and control of hypercholesterolaemia based on risk-specific LDL-C goal were determined, including the use of lipid-lowering therapy (LLT). Cox-regression models were used to identify predictors of LDL-C above goal among those who were aware and unaware of hypercholesterolaemia. Results: One thousand five hundred and sixty-eight (30.8%) participants were aware of hypercholesterolaemia and 877 (17.3%) were newly diagnosed (unaware). For those who were aware, 39.3% participants received LLT. Among those with 2 risk factors, only 59.7% attained LDL-C goal. The majority of them were taking statin monotherapy, and the median dose of statins was similar across all CHD risk categories. Among participants with 2 risk factors and not receiving LLT, 34.1% would require LLT. Malays or Asian-Indians, higher CHD risk category, increasing body mass index (BMI), current smoking and lower education status were associated with higher risk of LDL-C above goal. Being on LLT reduced the risk of having LDL-C above goal. Conclusion: The burden of hypercholesterolaemia is high in this multi-ethnic population especially those in the higher CHD risk categories, and might be partly contributed by inadequate titration of statins therapy. Raising awareness of hypercholesterolaemia, appropriate LLT initiation and titration, weight management and smoking cessation may improve LDL-C goal attainment in this population.

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Key words: Asians, Awareness, Cholesterol, Goal attainment, Prevalence ratio, Treatment

Introduction

Coronary heart disease (CHD) is emerging as the leading cause of death among Asian countries.[1] Changes in the CHD risk factors, in particular the rising prevalence of hypercholesterolaemia, have been implicated in the rising incidence of CHD in the Asia-Pacific region.[2] In a cross-sectional population study conducted in Beijing, China between 1984 and 1999, rising total cholesterol levels could explain 77% increase in the additional CHD mortality.[3] In addition to the changes in the dietary preferences (i.e. towards Western diet), they showed that the prescribing level of lipid-lowering treatment was suboptimal despite the rising burden of CHD. By contrast, in the Western countries, a reduction in the burden of CHD has been observed, and was associated with improvements in traditional risk factors, particularly total cholesterol levels.[4]

Detailed analyses from randomised controlled trials provided unequivocal evidence that treatment targeted at elevated low-density lipoprotein cholesterol (LDL-C) levels resulted in a significant reduction in cardiovascular events and mortality.[5-7] In addition, it has been shown that the greater the LDL-C lowering, the greater the reduction in CHD and mortality.[8-11] Although most studies reported a similar relative risk reduction for a given reduction in LDL-C

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levels, the absolute risk reduction is related primarily to an individual's absolute risk and to the absolute reduction in LDL-C levels achieved.[12] This information is critical to guide the implementation of evidence-based practice in routine clinical setting that determines optimal individual care for hypercholesterolaemia. In line with this, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) guidelines provide clear recommendations on treatment initiation, options and importantly the treatment goal for LDL-C level for both primary and secondary prevention of CHD.[13]

Existing population data on the prevalence of hypercholesterolaemia among Asian countries are based on the assessment of total cholesterol levels without taking into account a global cardiovascular risk assessment.[1] While important, this tells us little about the treatment gap between what is recommended in the guidelines and what is occurring in the population. In the REALITY-Asia study, among 2622 patients with hypercholesterolaemia recruited from 6 Asian countries, the LDL-C goal attainment was unsatisfactory, in particular those with CHD and diabetes mellitus.[14] The majority of patients were recruited by physicians (41% cardiologists), at high risk of CHD (90.2%), and the differences in practice patterns across centers limit the generalisability of its findings. To address this issue, we examined the prevalence, treatment and control of hypercholesterolaemia based on the NCEP-ATPIII guidelines in an Asian population living in Singapore. In addition, we also identified predictors of LDL-C above goal in the attempt to address the shortfalls in LDL-C goal attainment.

Materials and Methods

This cross-sectional study used data from the Singapore Prospective Study Program (SP2), which was a follow-up of 4 cross-sectional studies conducted in Singapore from 1982 to 1995. The details of the study population have been described previously.[15] Briefly, we invited 10,445 subjects from 4 population-based, Thyroid and Heart Study 1982 – 1984, the National Health Survey 1992, the National University of Singapore Heart Study 1993 – 1995 and the National Health Survey 1998 to participate in a repeat examination from 2004 to 2007.[16-19] Only the data from the follow-up component were analysed for this study.

All studies included a random sample of individuals from the Singapore population, with disproportionate sampling stratified by ethnicity to increase the number in the minority ethnic groups (Malays and Asian-Indians). Subjects deceased at the time of follow-up (as shown by data linkage to the Registry of Births and Deaths) were excluded (n = 517). Also excluded were 6 subjects who had emigrated and 85 who had errors in the records regarding their identity card number.

Subjects were contacted to obtain an appointment for investigators to administer the questionnaire at the subject's home. Three home visits were made on 3 different occasions, including one weekend and weekday, before a subject was deemed non-contactable. After this procedure was completed, 2673 subjects were non-contactable. Of those subjects who could be contacted, 30 (0.3%) refused to participate. All subjects were invited to attend a health examination for additional tests and collection of biologic specimens shortly after the home visit. A total of 7742 (74.1% response rate) subjects completed the questionnaire. Of these, 5129 also attended the health screening. Ethics approval was obtained from 2 institutional review boards (the National University of Singapore and the Singapore General Hospital). Informed consent was obtained before study was conducted.

Data Collection

Data on demographic and lifestyle factors (alcohol consumption, smoking), as well as medical history (including physician-diagnosed hypertension, diabetes mellitus, and hypercholesterolaemia, CHD and cancers) were collected by using interviewer administered questionnaires. For the health examination, participants were examined in the morning following a 10-hour overnight fast. Venous blood was drawn and collected in plain and fluoride oxalate tubes and was stored at 4°C for a maximum of 4 hours prior to processing. All biochemical analyses of blood were performed at the National University Hospital Referral Laboratory, which is accredited by the College of American Pathologists. Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) were measured using an automated autoanalyzer (ADVIA 2400; Bayer Diagnostics, New York). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.[20] Plasma glucose was assayed with enzymatic methods (ADVIA 2400). The intra- and inter-day coefficients of variation for total cholesterol, triglyceride, and HDL-C were 0.80% to 1.57% and 0.93% to 1.15%, 0% to 3.85% and 1.27% to 3.40%, 0.56% to 0.65% and 1.18% to 2.00% respectively.

Height was measured without shoes by using a wall mounted stadiometer. Weight was measured in light clothing by using the same digital scale (SECA, Vogel & Halke, Hamberg, Germany). An automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) was used to take 2 blood pressure readings from participants after 5 minutes of rest. Mean values of the closest 2 readings were calculated. Ankle-brachial index (ABI) was calculated

as the ratio of the higher of the 2 systolic pressures (from posterior tibial and dorsalis pedis) at the ankle to the average of the right and left brachial artery pressures.

Definitions

Participants who answered "Yes" to the question "Have you ever been told by a doctor (western trained) you have high blood pressure or diabetes?" were classified as having a history of hypertension or diabetes mellitus respectively. Diabetes mellitus was further defined as fasting plasma glucose ≥7.0 mmol/L or currently taking anti-diabetic agents. Hypertension was further defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or currently taking anti-hypertensive medications. Smoking was classified as never smoke, ex-smoker or current smoking. Alcohol intake was defined as alcohol consumption of more than 3 days a week. Marital status was classified as single, married, widow or divorced. Education status was classified as education attained up to primary school (≤6 years of formal education), secondary school (≤12 years of formal education) and diploma or higher (degree or PhD). Physical activity levels was categorised into tertiles as low, moderate and high based on MET/hour per week activity scores. Family history of premature CHD was defined as CHD in male first degree relative <55 years or female first degree relative <65 years. Data on lipid-lowering treatment (LLT) was derived from direct interviewer assessment of participants' medications and included use of statins, fibrate, niacin, ezetimibe and bile acid resins. Peripheral arterial disease (PAD) was defined as an ABI of ≤0.9.

The Framingham risk score (included age, sex, total and HDL cholesterol, smoking, and blood pressure) was used to determine the 10-year risk of CHD.[21] Participants were then assigned to one of the 4 risk categories according to the NCEP-ATPIII CHD risk determinants to determine qualification for LLT and specified treatment goals (Table 1).[13] Participants with physician-diagnosed hypercholesterolaemia were defined as aware of hypercholesterolaemia. Participants who had no previous history of hypercholesterolaemia, they would qualify as unaware of hypercholesterolaemia if the LDL-C levels were above CHD risk-specific goals.

Statistical Analysis

All data analyses were conducted using SPSS (version 13 SPSS Inc, Chicago). Means (Standard Deviation) and numbers and proportions (%) were used. All statistical tests were 2-sided, with a level of significance defined as $P<0.05$.

The assessment of risk factors for having LDL-C above goal was determined for participants who were aware and unaware of hypercholesterolaemia. To identify predictors for having LDL-C levels above goal, we estimated the proportion rate ratio (PRR) (95% Confidence Interval (CI)) associated with body mass index (BMI), ethnic group, socioeconomic factors (marital status, education status, physical activity, smoking status and alcohol consumption), and Framingham CHD risk group. Being on LLT was assessed as a factor only for those who were aware of hypercholesterolaemia. An individual with LDL-C above goal was defined as an individual having LDL-C levels above the CHD risk-specific LDL-C goals.

For the assessment of the control of hypercholesterolaemia, participants who were aware of hypercholesterolaemia were further divided into 2 groups: (i) those who were not receiving LLT, and (ii) those who were receiving LLT. For participants who were not receiving LLT, we determined the proportion of participants who attained risk-specific LDL-C goals, who would require initiation of LLT, and who would qualify for therapeutic lifestyle changes (TLC). Among participants who received LLT, we determined the proportion of participants who had LDL-C above treatment goals.

We also examined the median dose of commonly prescribed statins among participants who were receiving LLT. Kruskal-Wallis one way analysis of variance was used to examine whether the median dose for the statin therapy differed across the 4 CHD risk categories.

Table 1. LDL Cholesterol Goals and Cut-points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Group	Risk Category	LDL-C Goal (mg/dL)	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL-C Level at Which to Consider Drug Therapy (mg/dL)
1	0 to 1 Risk factor	<160	≥160	≥190
2	2+ Risk factors (10-year risk <10%)	<130	≥130	≥160
3	2+ Risk factors (10-year risk 10% to 20%)	<130	≥130	≥130
4	CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130

LDL-C: low-density lipoprotein cholestrol; CHD: Coronary heart disease

Table 2. Demographic Characteristics of Participants, Combined and by Ethnic Groups, Who Either Completed Questionnaire Only, Both Questionnaire and Health Screening and Questionnaire and Health Screening

	Total	Subjects who completed questionnaire only	Subjects who completed questionnaire and health screening
n	7742	2603	5083
Male, %	47.1	45.5	47.9
Race,%			
Chinese	64.6	60.5	66.6
Malay	49.5	23.7	17.4
Indian	15.9	15.8	16.0
*Current smoking, %	11.9	13.9	12.1
History of hypertension, %	22.5	23.8	21.8
History of diabetes mellitus,%	10.5	12.8	7.1
Age, year	49.8 ± 12.6	49.3 ± 13.9	50.1 ± 11.8

Data are expressed as mean (standard deviation) or % (proportion of the group).
*Defined as a yes response to the questions: "Have you ever smoked cigarettes?" and "Do you smoke now?"

Results

We excluded 3 participants who reported "other race" and 53 participants missing LDL-C results. Thus, the analyses included 5083 participants who completed both questionnaire and attended the health screening (65.7% of those who responded to questionnaire). The mean (SD) age was 50.1 (11.8) years, ranged from 24 to 95 years. Notably, participants who completed questionnaire and health screening were less likely to smoke, had lower prevalence of hypertension or diabetes mellitus, and lower proportion of Malay ethnicity compared to participants who completed questionnaire only (Table 2).

Overall, 2762 (54.3%) participants had 0 to 1 risk factor (low-risk), 1033 (20.3 %) had 2+ risk factors and 10-year risk <10% (intermediate low-risk), 454 (8.9%) had 2+ risk factors and 10-year risk 10% to 20% (intermediate high-risk), and 834 (16.4%) had 2+ risk factors and 10-year risk >20%, CHD or CHD risk equivalent (high-risk).

Based on CHD risk-specific LDL-C levels, we identified 2445 participants (48.1% of the study population) with hypercholesterolemia. Among these, 1568 (30.8% of the study population) participants were aware, and 877 (17.3% of the study population) were unaware of hypercholesterolaemia.

Table 3 shows the proportion of participants who were at or above LDL-C goal for those who were on LLT, or not on LLT. Among participants who were aware of hypercholesterolaemia, only 616 (39.3%) participants received LLT (17.9% in low-risk, 49.0% in intermediate low-risk, 42.0% in intermediate high-risk and 61.3% in high-risk category). Among those on LLT and with 2 risk factors, only 302 (59.7%) met their risk-specific LDL-C goals. The LDL-C goal attainment was lower with higher CHD risk categories such that only 44.3% were at LDL-C goal in the highest risk category. Among participants with 2 risk factors and not on LLT, 779 (42.9%) were at LDL-C goal, 417 (23.0%) would require TLC and 619 (34.1%) would require LLT initiation.

Next we examined the predictors of LDL-C above goal among participants who were aware and unaware of hypercholesterolaemia (Table 4). Overall, increasing BMI and Framingham risk score, and Malay and Asian-Indian ethnic groups were associated with greater risk

Table 3. Proportion of Participants Who Met LDL-C Goal for Those Who Were or Were Not on Lipid-Lowering Treatment Based on the NCEP-ATPIII Guidelines

	Total (n = 5083)	0 to 1 Risk Factor (n = 2762)	2 Risk Factors (Framingham 10-year Risk <10%) (n = 1033)	2 Risk Factors (Framingham 10-year Risk 10% to20%) (n = 454)	2 Risk Factors (Framingham 10-year Risk >20%) or CHD Equivalent (n = 834)
On LLT					
At LDL-C goal	397 (64.4%)	95 (86.4%)	150 (75.4%)	44 (69.8%)	108 (44.3%)
Above LDL-C goal	219 (35.6%)	15 (13.6%)	49 (24.6%)	19 (30.2%)	136 (55.7%)
Not on LLT					
At LDL-C goal	3154 (70.6%)	2375 (89.6%)	462 (55.4%)	187 (47.8%)	130 (22.0%)
Need TLC	639 (14.3%)	222 (8.4%)	251 (30.1%)	0	166 (28.1%)
Need LLT	674 (15.1%)	55 (2.1%)	121 (14.5%)	204 (52.2%)	294 (49.8%)

Data are expressed as n and % (proportion of the group).
LLT: Lipid lowering therapy; TLC: Therapeutic lifestyle changes; LDL-C: low-density lipoprotein cholesterol; CHD: coronary heart disease

Table 4. Risk Factors for LDL-C Above Goal Among Participants Who Were Aware and Not Aware of Hypercholesterolemia

Parameters	Aware of hypercholesterolemia (n = 1568)		Unaware of hypercholesterolemia (n = 3515)	
	Unadjusted PRR (95% CI)	Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	Adjusted‡ PRR (95% CI)
BMI (kg/m^2)	1.03 (1.01 – 1.04) †	1.02 (1.00 – 1.04) †	1.06 (1.04 – 1.07) †	1.05 (1.04 – 1.07) †
Ethnic group				
Chinese	1.0	1.0	1.0	1.0
Malay	1.41 (1.16 – 1.72) †	1.33 (1.07 – 1.65)*	1.77 (1.51 – 2.08) †	1.15 (0.97 – 1.38)
Indian	1.40 (1.16 – 1.69) †	1.38 (1.12 – 1.68) †	1.69 (1.42 – 2.01) †	1.24 (1.03 – 1.48)*
Marital status				
Single	1.0	1.0	1.0	1.0
Married	1.22 (0.89 – 1.67)	1.07 (0.77 – 1.47)	1.67 (1.31 – 2.14) †	1.05 (0.82 – 1.34)
Widow/Divorced	1.18 (0.79 – 1.75)	0.90 (0.59 – 1.36)	2.76 (2.03 – 3.73) †	1.38 (1.01 – 1.89)*
Education Status				
Primary	1.0	1.0	1.0	1.0
Secondary	0.938 (0.788 – 1.12)	0.89 (0.74 – 1.07)	0.76 (0.65 – 0.88)†	0.95 (0.81 – 1.10)
Tertiary (Diploma and higher)	0.699 (0.57 – 0.86)†	0.73 (0.58 – 0.91)*	0.40 (0.33 – 0.48)†	0.62 (0.51 – 0.77)†
Alcohol				
No	1.0	1.0	1.0	1.0
Yes (>3 drinks/week)	0.90 (0.76 – 1.09)	0.99 (0.82 – 1.20)	0.73 (0.62 – 0.87)**	0.91 (0.76 – 1.08)
Smoking status				
No	1.0	1.0	1.0	1.0
Ex-smoker	1.18 (0.49 – 2.84)	1.03 (0.42 – 2.51)	1.03 (0.53 – 1.98)	1.20 (0.62 – 2.36)
Current smoking	1.68 (1.35 – 2.09)†	1.51 (1.18 – 1.94)†	2.21 (1.87 – 2.61)†	2.08 (1.72 – 2.52)†
Physical activity levels				
Low	1.0	1.0	1.0	1.0
Moderate	1.06 (0.88 – 1.28)	1.09 (0.90 – 1.31)	0.91 (0.77 – 1.07)	1.03 (0.87 – 1.22)
High	1.07 (0.90 – 1.29)	1.00 (0.82 – 1.21)	0.99 (0.84 – 1.16)	1.03 (0.87 – 1.21)
Being on lipid-lowering therapy	0.78 (0.66 – 0.91)†	0.60 (0.50 – 0.71)†	-	-
Framingham risk group (10-year CHD risk)				
Low-risk (<10%)	1.0	1.0	1.0	1.0
Intermediate risk (10% to 20%)	1.40 (1.16 – 1.70)†	1.51 (1.23 – 1.84)†	2.88 (2.46 – 3.37)†	2.58 (2.20 – 3.03)†
High-risk (>20%)	2.07 (1.69 – 2.54)†	2.28 (1.84 – 2.82)†	4.63 (3.81 – 5.62) †	3.94 (3.22 – 4.82)†

*P <0.05, †P <0.005

‡Adjusted for all variables listed in the table.

PRR: Proportion rate ratio; CI: confidence intervals; BMI: body mass index

of LDL-C above goal. Among socioeconomic factors, current smoking was associated with higher risk, whereas higher education status was associated with lower risk of LDL-C above goal. Among participants unaware of hypercholesterolaemia, current alcohol intake (>3 drinks per week) was associated with lower risk, whereas being widow or divorced was associated with higher risk of LDL-C above goal. Physical activity was not a significant predictor of LDL-C above goal. Body mass index (BMI), Framingham risk score, ethnicity, education status and current smoking remained significant predictors for LDL-C above goal after multivariate adjustment. Among participants unaware of hypercholesterolaemia, the association for alcohol intake was no longer significant. However being widow or divorced remained a significant predictor with multivariate adjustment. Among those who were aware of hypercholesterolaemia, being on LLT reduced the risk of having LDL-C above goal.

Among those aware of hypercholesterolaemia, majority (71.4%) were taking statin monotherapy. The use of combination therapy (e.g. statin and fibrate) was low (3.7%). The median dose of statins therapy is shown in Table 5.

Table 5. Median (Range) Dose of Statins in Participants Aware of Hypercholesterolaemia by NCEP-ATPIII CHD-Risk Categories

	0 to 1 Risk Factor (n = 91)	2 Risk Factors (Framingham 10-year Risk <10%) (n = 171)	2 Risk Factors (Framingham 10-year Risk 10-20%) (n = 56)	2 Risk Factors (Framingham 10-year Risk >20%) or CHD Equivalent (n = 196)	*P**
Atorvastatin, mg	11.2 (5 – 20)	9.3 (2.5 – 20)	10.0 (5 – 15)	11.4 (10 – 20)	0.211
Lovastatin, mg	18.6 (10 – 40)	23.9 (10 – 60)	19.6 (10 – 40)	20.5 (5 – 60)	0.219
Simvastatin, mg	12.7 (5 – 20)	14.1 (2.5 – 80)	15.0 (5 – 40)	17.1 (5 – 60)	0.145
Pravastatin, mg	10.02	20.02	-	10.02	-
Rosuvastatin , mg	7.5 (5 – 20)	-	-	10.0 (10)	-
Vytorin†, mg	-	-	10/10‡	10/102	-

*Difference in the median statin dose across the risk categories using the Kruskal-Wallis one-way analysis of variance.

†Dose for Vytorin = simvastatin 10 mg and ezetimibe 10 mg

‡The range is not given as there is only one participant in the risk category group for that particular statin.

The median dose for commonly prescribed statins such as lovastatin, simvastatin and atorvastatin was 20.9 mg, 15.2 mg and 11.0 mg respectively. A Kruskal-Wallis test revealed no statistical difference in the median statin dose across the 4 CHD risk categories.

Discussion

Most studies in Asia have used a standard cut-off (e.g. total cholesterol 5.2 mmol/L) to define hypercholesterolaemia in all individuals. This is one of the few reports of the prevalence, treatment and control of hypercholesterolaemia in Asia that has taken into account the individual's CHD risk profile. This is important as both standard practice and evidence-based recommendations are supposed to be based on individual's risk of CHD to determine the levels of LDL-C for treatment initiation and goal. Thus, our study provides a better indication of the treatment gap that exists with respect to LLT for the prevention of CHD. To date, this has been reported only in China and in the REALITY-Asia study.[14,22]

Our study showed that a significant proportion of the population has high risk of CHD as assessed by the Framingham risk score and the NCEP-ATPIII CHD risk determinants. The prevalence of hypercholesterolaemia in this study population approximates 50% based on the NCEP-ATPIII risk determinants, with the proportion of those who were previously unaware of hypercholesterolaemia reaching 20%. Despite the wealth of evidence that LLT reduces CHD morbidity and mortality, only 39.6% of participants in the high-risk category reported taking LLT. In this category, even amongst those receiving LLT, less than half met the group-specific LDL-C treatment goals. In the lower risk categories, the proportion of individuals who were not on LLT, who nevertheless require it is relatively small. This is in agreement with findings from other investigators and likely reflects the higher threshold for treatment initiation and higher LDL-C goals in the lower risk categories.[14,23,24] But among those in the higher CHD risk categories, about 50% of those receiving LLT failed to attain LDL-C goals, and among those unaware of hypercholesterolemia, about 50% would require LLT initiation.

When considering predictors of LDL-C above goal, we observed that individuals who were aware of hypercholesterolaemia shared similar predictors as for those who were not aware of hypercholesterolaemia. Compared to Chinese, Malays and Asian-Indians had higher probabilities of having LDL-C above goal, despite being aware of hypercholesterolaemia. This finding might help to explain the observation from a previous study that showed Asian-Indians and Malays have poorer outcomes from myocardial infarction compared to Chinese.[25] Racial differences in the goal attainment and statin use was also reported among adults in United States (US) where non-Hispanic blacks and Mexican-American have higher rates of high LDL-C compared with non-Hispanic whites.[26] In addition, the finding of higher risk of LDL-C above goal in individuals with higher risk of CHD indicates suboptimal control which might be due to poor treatment vigilance as demonstrated by a similar median dose of commonly prescribed statins across all 4 CHD risk categories. In the REALITY-Asia study, there was very little change in the therapeutic approach over the 12-month study period despite LDL-C targets not being met.[14] Tay JC et al showed that in 523 patients with hypercholesterolaemia treated at the specialist out-patient clinics, majority did not achieve the recommended LDL-C goal; and this could be due to inappropriate use of type and dose of LLT, failure of titration and a high drug non-compliance rate.[27] The finding of higher

LDL-C goal attainment among those being on LLT further advocates the importance of appropriate use of LLT in the effort to improve LDL-C control in the population.[28]

Our study suggests that there are several potential socioeconomic and lifestyle factors that might influence LDL-C goal attainment. Among lifestyle factors, increasing BMI was an independent predictor of poorer LDL-C goal attainment. These associations have been shown with poorer blood pressure control in the Framingham Heart Study.[29] Obesity has a strong effect on lipoprotein metabolism and increased weight is a determinant of higher levels of triglycerides, elevated LDL-C, and low HDL-C.[30] Current smoking remained a strong predictor of LDL-C above goal after multivariate adjustment. In other studies, smoking is associated with higher LDL-C levels, more atherogenic lipoproteins and greater burden of atherosclerotic lesions.[31-33] In the Atherosclerosis Risk in Communities (ARIC) Study, smoking has been shown to increase the risk between LDL-C levels and CHD incidence.[34] Higher education status was associated with better LDL-C goal attainment. The reason for this observation is not clear, although intuitively it may be related to higher income levels, being better informed and having better access to healthy choice of diet. In support, the prevalence of obesity, diabetes, hypertension and heart disease are higher in individuals with lower education compared to their counterpart.[35] Although moderate alcohol intake is associated with more favourable lipids profiles, this factor was no longer a significant predictor of LDL-C goal after multivariate adjustment.[36] While physical activity was not a significant predictor of LDL-C goal attainment in this study, physical activity in combination with LLT reduces inflammatory mediators of atherosclerosis more markedly than LLT alone.[37] The association between marital status with higher risk of LDL-C above goal among those unaware of hypercholesterolemia is currently not clear. High-satisfying marriages have lower atherosclerotic burden than that of low-satisfying marriage or being single in the Healthy Women Study.[38] In the Trabzon Lipid Study, being widows or widowers was a significant independent predictor of dyslipidaemia.[39]

Our study also identified a substantial proportion of individuals with an absolute CHD risk which was intermediate and would qualify for TLC. TLC includes a reduction in the intake of saturated fats and cholesterol, weight reduction and increased physical activity. TLC/ Step 2 diet (7% saturated,10% monosaturated, 10% polyunsaturated and 75 mg cholesterol per 1000 kcal) and Mediterranean diet have been shown to lower LDL-C levels up to 30%.[13] Ueshima and co-workers reported that total cholesterol in Singapore is the highest among the selected Asian populations and attribute high total fat intake and higher prevalence of obesity to this observation.[1] Adopting diets that are low in saturated fat and cholesterol would lower LDL-C by an estimate of 11% to 15%.[40] A meta-analysis by Dattilo et al further showed that for every 1-kg decrease in body weight, the LDL-C level would decrease by 0.02 mmol/L.[41] This underscores the integral role of TLC in the overall CHD risk factors management.

Our study has some limitations. Our overall response rate was low (49%) and might limit its generalisation to this population. However, the lower prevalence of history of hypertension and diabetes mellitus in participants who attended all components of the study compared to those who only completed questionnaire suggests that this is a relatively healthier population. Thus our findings may have underestimated the prevalence of hypercholesterolaemia of the general population. The within person variation for calculated LDL-C levels can be as high as 8%.[42] Thus our single measurement of fasting cholesterol may have resulted in some misclassification on individuals' risk of CHD and subsequent treatment recommendation. However, single measurements are an acceptable alternative in large population-based studies and the misclassification is likely to be non-differential in nature.[43] We are not able to identify changes in therapy in the attempt to achieve treatment goals due to the cross-sectional design of this study, thus precluding us from investigating whether lack of adherence to statin therapy might have contributed to poor control. We also have not assessed the dietary influences on LDL-C goal attainment.

Conclusion

In summary, there is a high burden of hypercholesterolaemia in this population despite established evidence-based guidelines and treatment. There is a large treatment gap and inadequate control despite on LLT. Lack of awareness, lack of LLT and inadequate statins dose titration may contribute to this treatment gap. The scope of this problem is particularly marked among Malays and Asian-Indians. Among socioeconomic factors, increasing age and BMI are independent predictors of poorer LDL-C goal attainment, whereas higher education status is an independent predictor of LDL-C goal attainment. Among those unaware of hypercholesterolaemia, smoking increases the risk of LDL-C above goals. A strategy that improves knowledge about the use and adherence to the national guidelines among practitioners and patients, weight reduction and cessation of smoking would help to mitigate the burden of hypercholesterolaemia and the rising incidence of CHD in Asian population.

REFERENCES

1. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008;118:2702-9.
2. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003;32:563-72.
3. Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. Circulation 2004;110:1236-44.
4. Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G, et al. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. JAMA 2010;303:1841-7.
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
6. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349-57.
7. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22.
8. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
9. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.
10. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425-35.
11. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294:2437-45.
12. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
14. Kim HS, Wu Y, Lin SJ, Deerochanawong C, Zambahari R, Zhao L, et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. Curr Med Res Opin 2008;24:1951-63.
15. Nang EE, Khoo CM, Tai ES, Lim SC, Tavintharan S, Wong TY, et al. Is there a clear threshold for fasting plasma glucose that differentiates between those with and without neuropathy and chronic kidney disease?: the Singapore Prospective Study Program. Am J Epidemiol 2009;169:1454-62.
16. Cutter J, Tan BY, Chew SK. Levels of cardiovascular disease risk factors in Singapore following a national intervention programme. Bull World Health Organ 2001;79:908-15.
17. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein(a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. J Epidemiol Community Health 1997;51:394-9.
18. Hughes K, Yeo PP, Lun KC, Thai AC, Sothy SP, Wang KW, et al. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. J Epidemiol Community Health 1990;44:29-35.
19. Tan CE, Emmanuel SC, Tan BY, Jacob E. Prevalence of diabetes and ethnic differences in cardiovascular risk factors. The 1992 Singapore National Health Survey. Diabetes Care 1999;22:241-7.
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
21. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
22. Wu YF. [The second multi-center survey of dyslipidemia management in China: goal attainment rate and related factors]. Zhonghua Xin Xue Guan Bing Za Zhi 2007;35:420-7.
23. Clearfield MB. Underidentification and undertreatment of dyslipidemia. J Am Osteopath Assoc 2003;103:S5-8.
24. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000;160:459-67.
25. Mak KH, Chia KS, Kark JD, Chua T, Tan C, Foong BH, et al. Ethnic differences in acute myocardial infarction in Singapore. Eur Heart J 2003;24:151-60.
26. Hyre AD, Muntner P, Menke A, Raggi P, He J. Trends in ATP-III-defined high blood cholesterol prevalence, awareness, treatment and control among U.S. adults. Ann Epidemiol 2007;17:548-55.
27. Tay JC, Chee YC. Drug treatment of hypercholesterolaemia. Ann Acad Med Singapore 1998;27:794-9.
28. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. Ann Pharmacother 2008;42:1208-15.
29. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure : factors associated with lack of blood pressure control in the community. Hypertension 2000;36:594-9.
30. Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity : impact on cardiovascular disease. Circulation 1998;98:1472-6.
31. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. BMJ 1989;298:784-8.
32. Kim BJ, Hwang ST, Sung KC, Kim BS, Kang JH, Lee MH, et al. Comparison of the relationships between serum apolipoprotein B and serum lipid distributions. Clin Chem 2005;51:2257-63.
33. McGill HC, Jr., McMahan CA, Malcom GT, Oalmann MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 1997;17:95-106.
34. Hozawa A, Folsom AR, Sharrett AR, Payne TJ, Chambless LE. Does the impact of smoking on coronary heart disease differ by low-density lipoprotein cholesterol level?: the Atherosclerosis Risk in Communities (ARIC) Study. Circ J 2006;70:1105-10.
35. Paeratakul S, Lovejoy JC, Ryan DH, Bray GA. The relation of gender, race and socioeconomic status to obesity and obesity comorbidities in a sample of US adults. Int J Obes Relat Metab Disord 2002;26:1205-10.

36. Standridge JB, Zylstra RG, Adams SM. Alcohol consumption: an overview of benefits and risks. South Med J 2004;97:664-72.
37. Konig D, Deibert P, Winkler K, Berg A. Association between LDL-cholesterol, statin therapy, physical activity and inflammatory markers in patients with stable coronary heart disease. Exerc Immunol Rev 2005;11:97-107.
38. Gallo LC, Troxel WM, Kuller LH, Sutton-Tyrrell K, Edmundowicz D, Matthews KA. Marital status, marital quality, and atherosclerotic burden in postmenopausal women. Psychosom Med 2003;65:952-62.
39. Erem C, Hacihasanoglu A, Deger O, Kocak M, Topbas M. Prevalence of dyslipidemia and associated risk factors among Turkish adults: Trabzon lipid study. Endocrine 2008;34:36-51.
40. Fletcher B, Berra K, Ades P, Braun LT, Burke LE, Durstine JL, et al. Managing abnormal blood lipids: a collaborative approach. Circulation 2005;112:3184-209.
41. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992;56:320-8.
42. Bookstein L, Gidding SS, Donovan M, Smith FA. Day-to-day variability of serum cholesterol, triglyceride, and high-density lipoprotein cholesterol levels. Impact on the assessment of risk according to the National Cholesterol Education Program guidelines. Arch Intern Med 1990;150:1653-7.
43. Goff DC, Jr., Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. Circulation 2006;113:647-56.