Clinical Investigations

The Gender Differences in Baseline Characteristics and Statin Intervention Among Outpatients with Coronary Heart Disease in China: The China Cholesterol Education Program

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ABSTRACT

Background: The China Cholesterol Education Program (CCEP) aimed to investigate the baseline characteristics of outpatients with coronary heart disease (CHD) according to gender, especially lipid levels, statin intervention, and rates of achieving their goal low-density lipoprotein cholesterol (LDL-C) level.

Methods: A total of 4778 CHD outpatients were enrolled from 52 centers in 6 Chinese cities from January 2006 to January 2007.

Results: Female outpatients were significantly older than male outpatients (66±10 vs 63±11 years, $P<0.001$). Male outpatients were more likely to smoke than female outpatients ($P<0.001$). Female outpatients had a higher prevalence of hypertension, diabetes mellitus, LDL-C level, and total cholesterol level (all P values <0.001). About 82% of the participants received statin therapy. The LDL-C levels were 3.06±1.08 mmol/L and 2.89±0.97 mmol/L in outpatients at high risk and very high risk respectively ($P<0.001$). Though there were higher rates of statin intervention, only 36.2% of the high risk outpatients got to the target LDL-C level (<2.6 mmol/L); 10.9% of the very high risk outpatients achieved the optimal LDL-C level (<1.82 mmol/L) suggested by National Cholesterol Education Program Adult Treatment Panel III. The rate of achieving target was only 42.2%, even when LDL-C <2.6 mmol/L was the target level for patients at very high risk. Only 19.4% of the outpatients at very high risk achieved the target (LDL-C <2.08 mmol/L) suggested by the updated Chinese guideline for CHD.

Conclusion: Although the outpatients received a higher rate of statin therapy, the rates of achieving the target were lower. There is still a significant gap between the guidelines and clinical practice in statin intervention among these CHD outpatients, particularly for women.

Introduction

Coronary heart disease (CHD) is still a major worldwide threat.[1] Although several risk factors contribute to CHD, the Chinese Sino-Multiprovincial monitoring of the trends and determinants in cardiovascular diseases project and other studies have indicated that a higher lipid level is a major risk factor, especially the low-density lipoprotein cholesterol (LDL-C) level.[2–5] Several clinical trials indicate that for every 1% reduction in LDL-C level, relative risk for a major CHD event is reduced by approximately 1%.[6–12] Recently, many clinical epidemiologic trials have proved CHD patients or equivalent high-risk status could benefit from lowering of the LDL-C levels with statins. Recent clinical trials,[13–17] such as Heart Protection Study and Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysisin Myocardial Infarction 22 showed further benefit could be achieved by lowering the LDL-C level to well below 100 mg/dL in some patient populations.[6,18] According to those trials, setting an LDL-C goal of <70 mg/dL (1.82 mmol/L) for high risk patients must be left as a therapeutic option, whereas a goal of <100 mg/dL (2.6 mmol/L) can be retained as a strong recommendation. The China Cholesterol Education Program (CCEP) was prompted by the interest in investigating the characteristics of outpatients with CHD and statin intervention, rates of achieving the target LDL-C levels suggested by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[19] and the Chinese guidelines,[20] and providing evidence to encourage an improvement in management strategies in outpatients with CHD.

Methods

Study Population

This study involved 52 centers in 6 cities (see Appendix) in China. All participants were CHD outpatients and continuously enrolled from January 2006 to January 2007. Major

Clin. Cardiol. 32, 6, 308–314 (2009)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20514

Received: July 11, 2008
Accepted with revision: August 11, 2008

exclusion criteria included inpatients, a significant medical or surgical event (percutaneous coronary intervention, coronary artery bypass graft) in the last 3 months, or significant cardiac failure (New York Heart Association class III/IV), renal or hepatic disease, 1-diabetes mellitus (DM), or allergy to statins. Data were collected by questionnaires including demographic data, medical history, CHD diagnosis, treatment of CHD, and laboratory examinations.

Classification of Risk Category

Patients in the category of high risk were CHD patients with CHD risk equivalents which included noncoronary forms of atherosclerotic diseases, or DM.

Patients in the very high risk category were those with the presence of established cardiovascular disease plus (1) multiple major risk factors (especially DM), (2) severe and/or poorly controlled risk factors (continued cigarette smoking), (3) the multiple risk factors of metabolic syndrome, and (4) patients with acute coronary syndrome (ACS).

The data collection protocol was approved by the Beijing University Research Ethics Committee. All participants signed informed consent statements that allowed access to their medical records.

Statistical Analysis

All case record data were entered into 2 Epidata 3.02 (EpiData Association, Odense, Denmark) databases by different people. All analyses were performed with SPSS, version 13.0. (SPSS, Inc., Chicago, IL) Continuous variables were expressed as mean±SD, and discrete variables as percentages. The differences in continuous variables between groups were examined by a t test. The differences in discrete variables between groups were calculated by the Pearson χ^2 test.

Results

A total of 4778 CHD outpatients were enrolled. The baseline demographics of CHD outpatients is shown in Table 1. Most of the participants were male (n = 3059, 64%). The female outpatients were significantly older than the male ($P<0.001$). There was significant difference in systolic blood pressure between female and male outpatients ($P<0.001$). The male outpatients were much more likely to smoke than the female outpatients (24.6% vs 3.3%, $P<0.001$).

Table 2 illustrates disease history. The most frequent disease was dyslipidemia (78.5%). Hypertension was also common in both male (64.8%) and female outpatients (76.2%). The female outpatients more often had hypertension, DM, peripheral artery disease, noncoronary forms of atherosclerosis disease, and dyslipidemia. There was no significant difference between the proportions of stroke in both sexes ($P = 0.170$).

The baseline interventions of the medicines which were used to control risk factors are illustrated in Table 3. An average of 69.4% of outpatients were using nitrates, 91.2% were using anti-platelet drugs, 63.8% were using beta receptor blocker, 44.3% were using angiotensin-converting enzyme inhibitors, and 82.2% were using statins. No significant difference was found between the proportions of using statins in either group ($P = 0.367$).

Table 1. Baseline Demographic Data of CHD Outpatients

	Male (n = 3059)	Female (n = 1719)	Total (n = 4778)	*P* Value
Age (yr)	63 ± 11	66±10	64±11	<0.001
35-45yrs (n)	151	32	183	—
45-55yrs (n)	600	203	803	—
55-65yrs (n)	816	469	1285	—
65-75yrs (n)	987	702	1689	—
75-85yrs (n)	452	283	735	—
85-95yrs (n)	53	30	83	—
BMI (kg/m²)	24.6±2.9	24.7±3.4	24.6±3.1	0.160
SBP (mm Hg)	131±18	134±18	132±18	<0.001
DBP (mm Hg)	78±11	79±11	79±11	0.224
Smoking status (%) (never/former/current)	42.9/32.5/24.6	93.5/3.2/3.3	61.2/21.9/16.9	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Current Medical History and Family Diseases

	Male (n = 3059)	Female (n = 1719)	Total (n = 4778)	*P* Value
Current diseases (%)				
Hypertension	64.8	76.2	68.9	<0.001
DM	21.2	25.3	22.7	0.001
Stroke	10.2	11.5	10.7	0.170
PAD	11.7	14.0	12.5	0.021
Non-coronary forms of atherosclerotic disease	19.9	22.8	21.0	0.022
Dyslipidemia	76.2	82.6	78.5	<0.001
Family diseases (%)				
Hypertension	36.9	40.0	38.0	0.035
DM	13.6	14.7	14.0	0.271
Stroke	14.4	13.6	14.1	0.444
CHD	23.2	25.9	24.2	0.034

Abbreviations: DM, diabetes mellitus; PAD, peripheral arterial disease; CHD, coronary heart disease.

The most frequent statin prescribed in China was atorvastatin (43.8%). The average dose of atorvastatin was 15.9 mg in men and 16.5 mg in women. Simvastatin was also used frequently (Table 4).

As demonstrated in Table 5, the average level of LDL-C was 2.93 mmol/L; the LDL-C level in female outpatients was 3.13 mmol/L. The baseline levels of TC, LDL-C, and high-density lipoprotein cholesterol (HDL-C) in female outpatients were significantly higher than that of male outpatients ($P<0.001$).

All outpatients were classified into a high risk group (n = 1171) and a very high risk group (n = 3607) according to NCEP ATP III.[19] The mean LDL-C level in patients at high risk was 3.06 mmol/L, and 2.89 mmol/L in patients at very high risk ($P<0.001$). Of the 1171 patients at high risk, 81.4% of them had accepted statin therapy, statins were also used in 82.5% of the very high risk outpatients ($P = 0.382$). But Table 6 illustrates that only 36.2% of the high risk patients got to the target LDL-C level (<2.6 mmol/L), 10.9% of the very high risk patients achieved the optimal LDL-C level (<1.82 mmol/L). In the 4 categories, the rates of achieving target goals were 12.3%, 11.6%, 8.4%, and 11.5% in patients with CHD plus (1) multiple major risk factors (especially DM), (2) severe and/or poorly controlled risk factors (continued cigarette smoking), (3) the multiple risk factors of the metabolic syndrome, and (4) patients with ACS, respectively.

The lowest rate and highest rate of achieving target goals are 5.7% and 74.2% in patients at high risk, and 4.0% and 43.4% in patients at very high risk, respectively. Even with the LDL-C level <2.6 mmol/L as the target in outpatients at very high risk, only 42.2% of those outpatients achieved the target. Only 19.4% of the outpatients at very high risk achieved the target (LDL-C <2.08 mmol/L) suggested by the updated Chinese guideline for chronic stable angina pectoris and acute coronary syndrome.[20,21]

Discussion

This is the first large-scale systematic availability of medical records and multicenter survey about the baseline characteristics, especially lipid levels and statin intervention in CHD outpatients sponsored by CCEP. CCEP represents multiple areas of China.

In this study, the female outpatient was significantly older than male outpatients. Male patients were more likely to smoke than female outpatients. Female outpatients had more risk factors to CHD compared with male outpatients, such as a higher prevalence of hypertension, DM, LDL-C level, and TC level (all *P* value ≤0.001). All those data showed there was a significant gender difference in outpatients with CHD. Recently, lots of studies have focused on the gender differences in CHD patients,[22–25] and confirm the strong relationship between lipoproteins and coronary heart disease development among women.[26] This study showed the gender differences among CHD outpatient characteristics.

The important treatment for CHD was statin intervention. The statin therapies were much higher in both sexes

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20514

Table 3. Intervention of TLC and Drugs in Outpatients

	Male (n = 3059)	Female (n = 1719)	Total (n = 4778)	*P* Value
TLC (%)	83.0	82.4	82.8	0.601
Nitrate (%)	70.6	67.1	69.4	0.012
Diuretics (%)	13.5	16.4	14.5	0.006
Anti-platelet drugs (%)	92.4	89.1	91.2	<0.001
BRB (%)	64.6	62.4	63.8	0.133
CCB (%)	35.3	45.4	38.9	<0.001
ACEI (%)	47.0	39.6	44.3	<0.001
ARB (%)	22.1	26.6	23.7	0.001
Statins (%)	81.9	82.9	82.2	0.367
Fibrates (%)	4.7	5.1	4.9	0.620
Hypoglycemic drugs (%)	18.0	20.3	18.9	0.056

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BRB = beta-blocker; CCB = calcium channel blocker; TLC = therapeutic lifestyle changes.

Table 4. Doses of Lipid Lowing Medicines

Statins	Male (n = 3059)	Female (n = 1719)	Total (%)	Total (n = 4778)
Atorvastatin	15.9±6.7	16.5±6.4	43.8%	16.1±6.7
Simvastatin[a]	20.6±7.6	22.3±9.7	19.5%	21.2±8.4
Pravastatin	19.7±5.0	19.6±5.2	11.7%	19.6±5.1
Fluvastatin	38.2±5.7	38.4±5.4	4.7%	38.3±5.6
Lovastatin	26.3±10.4	24.2±10.2	1.3%	25.7±10.3
Others	28.0±47.8	32.3±51.0	1.2%	30.0±48.5
Fibrates				
Fenofibrate	204.4±29.8	200.0±0.0	1.9%	203.1±24.8
Gemfibrozil	300.0±0.0	300.0±0.0	0.6%	300.0±0.0
Bezafibrate	200.0±0.0	200.0±0.0	0.1%	200.0±0.0
Others	500.0±0.0	500.0±0.0	0.3%	500.0±0.0

[a]*P* = 0.005 between male and female outpatients, others are not significant.

(men vs women, 81.9% vs 82.9%, $P>0.05$). A total of 82.2% of all the participants received statin therapy. The rate of statin therapy was higher than the result in Japan (36.3%).[27] A study of Hong Kong showed only 37% of the participants received the lipid lowering drugs.[28] Cooke and Hammerash's study reported lipid lowering therapy was only prescribed to 68.6% of their patients, with no significant sex differences (men vs women, 71.4% vs 63.3%).[24] Our result was also higher than the results of small trials in China and other reports.[29]

Recently, the benefits of lipid lowering treatment have been well documented.[6–10,12,15] The NCEP recommended LDL-C goal is <100 mg/dl in high risk persons, and <70 mg/dl is a therapeutic option in very high risk persons.[19] The beneficial effects may be related to plaque stabilization, reductions in inflammatory cell activity, platelet activation, thrombus formation, and improvement

Table 5. Baseline Laboratory Examination Characteristics of Outpatients

Baseline Characteristics	Male	Female	Total	*P* Value
TC (mmol/L)	4.80±1.50	5.21±1.53	4.95±1.52	<0.001
TG (mmol/L)	1.84±1.04	1.95±1.10	1.88±1.07	0.001
HDL-C (mmol/L)	1.20±0.44	1.32±0.49	1.24±0.46	<0.001
LDL-C (mmol/L)	2.81±0.95	3.13±1.07	2.93±1.00	<0.001
Glucose (mmol/L)	5.86±2.25	6.13±2.79	5.96±2.46	<0.001
ALT (U/L)	27.63±16.28	23.69±13.85	26.20±15.55	<0.001
AST (U/L)	36.39±55.34	32.42±47.18	34.96±52.57	0.015
CK (u/L)	140.8±324.48	108.98±246.75	129.23±299.25	0.001
HbA_{1C} (%)	6.27±2.16	6.55±2.24	6.25±2.20	0.072
BUN (mmol/L)	6.18±2.14	6.02±2.18	6.12±2.15	0.070
CRE (umol/L)	85.29±31.79	80.72±30.01	83.77±31.30	<0.001
UA (mmol/L)	342.98±102.22	312.52±102.11	335.91±103.17	<0.001

Abbreviations: TC, total cholesterol; TG, total glycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatine kinase; BUN, blood urea nitrogen; CRE, creatine; UA, uric acid.

Table 6. LDL-C Levels According to the Risk Category

Risk Category	LDL-C Level	Total Rate of Achieving the Target (%)	Male (%)	Female (%)	*P* Value
High risk (n = 1171) (LDL-C: 3.06±1.08 mmol/L)	<1.82 mmol/L	36.2	14.7	5.7	<0.001
	1.82-2.6 mmol/L		30.8	22.8	<0.001
	≥2.6 mmol/L		54.5	71.5	<0.001
Very high risk (n = 3607) (LDL-C: 2.89±0.97 mmol/L)	<1.82 mmol/L	10.9	11.9	9.0	<0.001
	1.82-2.6 mmol/L		33.9	26.1	<0.001
	≥2.6 mmol/L		54.2	64.9	<0.001

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

in endothelial function.[30–32] Lipid lowering therapy was widely accepted by the Chinese cardiologists to modify the risk factors to CHD.

Although most of the outpatients received lipid lowering therapy in both high risk and very high risk groups, the rates of achieving goals were low in both groups (Table 6). The rate of achieving the target goal was only 42.2%, even when LDL-C <2.6 mmol/L was the target level for patients at very high risk. The rates of achieving goal were much lower compared with the rates of statin intervention.

China published an updated guideline for CHD in 2007, a LDL-C level <2.08 mmol/L was recommended in patients with CHD.[20,21] Even so, only 19.4% of the outpatients at very high risk achieved the target.

Reports showed the rate of achieving the target in patients with coronary heart disease was 29.9% in Japan[27] and 15% in Hong Kong.[28] Cooke and Hammerash's study indicted of the patients prescribed lipid lowering therapy (primarily statins), 53.8% of them achieved target (LDL-C of <2.60 mmol/L.[24] However, all the success rates were much lower.

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The NCEP report was well accepted by most of the China cardiologists in recent years. There is progress in awareness, treatment, and control of dyslipidemia, although substantial proportions of women (and men) remain untreated or undertreated in China, especially in women whose rates of LDL-C were significantly lower than that of men. The possible reasons included: doctors paid more attention to the outpatients, but there was no good follow-up for the LDL-C level. All the doses of statins were moderate doses; maybe more intensive LDL-C lowering therapy should be recommended in those outpatients to reach the goals. Different statins had different effects in lowering LDL-C; maybe some statins were not compatible with all the outpatients. Though the LDL-C level was higher than the goals, maybe the reduction of LDL-C level was larger than 30% in some outpatients; and the adherence of outpatients should also be investigated. Another point that should be looked into is whether Chinese practitioners are hesitant to prescribe statins or give intensive statin intervention because of concern over the safety of statins. Hence, there is still a significant gap between the guidelines and clinical practice in statins intervention among these CHD outpatients, particularly for women.

There are several limitations to our study. Firstly, this is only a cross-section study, and it only represents large cities in China. Secondly, the rates of achieving the target were low; while we cannot find the exact reasons for this, several reasons may be responsible.[33] A follow-up study will focus on these points.

Acknowledgments

The involvement of the study coordinators and their hospitals are acknowledged (see Appendix). The study was supported by Pfizer Pharmaceuticals, Ltd. (New York, NY).

Appendix

Shanghai Yawei Xu; Daifu Zhang; Mingzhong Zhao; Guoping Lu; Yongwen Qin; Zonggui Wu; Jianping Liu; Junbo Ge; Baogui Sun; Haiming Luo; Minghe Wang; Yigang Li; Dadong Zhang; Shufu Zhang; Jianrong Zhao; Huigen Jin; Haiming Shi; Qiliang Liu; Meixian Jiang; Ning Zhu.

Beijing Dayi Hu; Xiaowei Yan; Shuixiang Yang; Qing He; Buxing Chen; Mingsheng Wang; Yong Huo, Meilin Liu; Ming Feng; Zhe Qi; Fenghe Du; Lizhi Ke, Feng He; Zhaozhong Liu; Dong Shen; Xiaofei Wang; Bin Wang; Xiaoping Xiang; Jinghua Liu; Yuannan Ke, Zhigang Zheng; Xian Wang; Wei Gao; Yang Wu; Hongxu Liu; Hongwei Li; Huayi Sun; Huiliang Liu.

Guangzhou Pingsheng Wu; Guanglian Li; Yingling Zhou; Xugang Dong.

Xinjiang Jianxin Lei; Gang Wu; Maoru Ma.

Zhejiang Shenghuang Wang; Shijun Ge; Hang Chen; Huaiqin Zhang; Jun Wang; Geng Xu; Ningfu Wang; Guosheng Fu; Zhaoquan Huang; Farong Shen.

Tianjin Yaomin Sun; Tiemin Jiang; Shuzhong Chen.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20514 © 2009 Wiley Periodicals, Inc.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20514