Statins usage and target achievement of LDL-C level in Chinese patients with coronary artery disease impacted by 2013 ACC/AHA cholesterol guideline

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Abstract
Background: Hypercholesterolemia is the accepted causal risk factor for atherosclerotic cardiovascular disease (ASCVD). 2013 ACC/AHA guideline on the treatment of cholesterol advised to tailor high-intensity statin for patients with coronary artery disease (CAD). However, its impact of real clinical practice has not been examined in China.

Methods: In this cross-sectional study, 3592 patients with CAD were consecutively enrolled who were receiving statins in outpatient department (at least 4 weeks) before they were admitted to the ward at five University hospitals from April 2011 to December 2015. Patients were divided into two groups according to the admission time before (group A, n = 1521) or after (group B, n = 2071) online announcement date of 2013 ACC/AHA guideline. The situation of statin application and LDL-C target achievement (LDL-C < 1.8 mmol/L) in both groups were compared.

Results: Data indicated that the constituent ratio of different kinds of statins usage was significantly different between the two groups (< 0.05), and the proportion of rosuvastatin application grew up in group B ( 20.00%) when compared with group A (10.50%, p < 0.05). However, the mean dosage of atorvastatin or rosuvastatin had no significant change. More importantly, the achievement of LDL-C target in both groups was still extremely low (27.9% in group A vs. 26.9% in group B, p = 0.5077).

Conclusion: No much change of clinical practice with regard to cholesterol management was found in Chinese patients with CAD, accompanied by very low achievement of LDL-C target, suggesting that there is a great room for the improvement of cholesterol control in Chinese patients with CAD.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide [1]. Low-density lipoprotein cholesterol (LDL-C) is the first cause for atherosclerotic vascular disease (ASCVD). Undoubtedly, numerous evidences from randomized clinical trials (RCTs) have been demonstrated that cholesterol-lowering therapy can reduce the mortality of ASCVD [2]. Statins are widely used and have been proven to be effective in the prevention of ASCVD events, primarily by reducing plasma LDL-C concentrations. Unfortunately, the incidence of ASCVD is still increasing not only in developed countries, but also in the developing countries, especially in China, even in the era of statin [3–5].

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA), released the revised cholesterol management guideline in 2013 [6]. The 2013 ACC/AHA guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults represents a major shift from prior cholesterol management guideline. The new guideline includes data from individual randomized trials as well as the most comprehensive meta-analyses. The 2013 ACC/AHA guideline emphasized the important meaning of cholesterol-lowering therapy in primary and secondary prevention of ASCVD. Some new
opinions were expressed in the new guideline, for example, the category of statins according to their ability of lowering LDL-C. Statins were defined as high-intensity, moderate-intensity and low-intensity statins. The guideline has a broader focus on risk of ASCVD including stroke, and identify four statin benefit patient groups that benefit from either “high-intensity” or “moderate-intensity” statin therapy rather than LDL-C or non-HDL-C targets. The four major statin benefit patient groups include 1) individuals with clinical ASCVD; 2) primary elevations of LDL-C ≥ 190 mg/dL; 3) diabetics aged 40–75 years with LDL-C 70–189 mg/dL and without clinical ASCVD; and the guideline recommended that high-intensity statins should be used in those patients who are diagnosed as ASCVD with age 40–75, whatever the baseline level of LDL-C. It is unknown that the impact of 2013 ACC/AHA guideline on the clinical practice of the cardiologists in real world in China.

In this study, therefore, we tried to investigate the impact of the 2013 ACC/AHA guideline on the statin prescriptions of cardiologists for those patients with CAD using multiple center manner. At the same time, we also analyzed the LDL-C target achievement between the patients who took statins before the announcement of 2013 ACC/AHA guideline and those patients who were prescribed statins after the announcements of the guideline.

2. Methods

2.1. Study population

We enrolled consecutively 3952 patients with confirmed diagnosis of coronary artery disease (CAD) who were receiving statins in outpatient department before they were admitted to the ward at five University hospitals from April 2011 to December 2015. These patients were divided into the two groups according to the admission time before (group A, n = 1521) or after (group B, n = 2071) online announcement date of 2013 ACC/AHA guideline. We analyzed the situation of different kinds of statins application and the difference of average level of LDL-C after treatment of statins between the two groups. We also made an analysis about the change of the control rate of LDL-C < 1.8 mmol/L in both groups. Including criteria: age 18–75 years old, males or females, angiography-proven CAD, and taking statin every day for at least 4 weeks. Excluding criteria: age < 18 or > 75 years old, normal coronary artery, no statin therapy or intermittent taking statin for less than 4 weeks. Patients with previous acute coronary syndrome within 1 month, serious heart failure or arrhythmia, infectious disease within 1 month, serious liver or renal dysfunction, autoimmune disease, malignant disease, pregnancy or lactation, or a psychiatric disorder were also excluded from the study. CAD was defined as at least one main coronary artery stenosis ≥ 70% by coronary angiography. Hypertension was defined as BP ≥ 140/90 mm Hg or taking anti-hypertensive medicines. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L, random glucose ≥ 11.1 mmol/L, or OGTT 2 h glucose ≥ 11.1 mmol/L or taking anti-hyperglycemia medicines.

2.2. Statin therapy classification

Statins in Chinese market include simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin and lovastatin (XueZhiKang). Based on 2013 ACC/AHA guideline on the treatment of cholesterol, we classified statin intensity: (1) high-intensity (atorvastatin 40–80 mg, rosuvastatin 20–40 mg); (2) moderate-intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, fluvastatin 80 mg, pitavastatin 2–4 mg) and (3) low-intensity (simvastatin 10 mg, pravastatin 10–20 mg, fluvastatin 20–40 mg).

2.3. Blood lipid measurements

Blood samples were obtained from the cubital vein after an overnight fasting. All samples were analyzed after thawing within the first 24 h of the hospital admission. The concentrations of serum TC, TG, HDL-C and LDL-C were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) [7]. LDL-C was calculated using the Friedewald equation [(TC-TG)/2.2], unless TG were elevated (>4.5 mmol/L). Based on the guideline of 2010ESC/EAS cholesterol management, the target of LDL-C level was defined as < 1.8 mmol/L for very-high risk patients including patients with CAD [8].

2.4. Statistical analyses

Data are presented as mean ± SD, median with interquartile ranges, or frequencies with percentages, as appropriate. We used the chi-square test to assess whether proportions were statistically significant. The level of significance was established a priori at 2-sided p < 0.05. All patients provided informed consent and each enrolling center obtained institutional review board approval. All analyses were performed using Statistical analysis was performed with SPSS version 19.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. General characteristics of the patients before and after the announcement of 2013 ACC/AHA guideline

The patients in group A were elder than in group B (58.24 ± 10.07 vs. 57.48 ± 9.82 years old, p < 0.05), the percentage of male patients was higher in group A (76.2% vs. 73.1%, p < 0.05), the percentage of dyslipidemia was higher in group A (79.2% vs. 74.8%, p < 0.05). The level of alanine transaminase (ALT), total bilirubin (TBIL) and direct bilirubin (DBIL) was no significantly different in both groups, except the level of aspartate aminotransferase (AST) in group A was higher than that in group B (22.37 ± 14.95 IU/L vs. 20.43 ± 14.05 IU/L, p < 0.05). The level of glucose was higher in group A than in group B (5.80 ± 1.72 mmol/L vs. 5.67 ± 1.62 mmol/L, p < 0.05). The level of creatinine was higher in group A than that in group B (79.20 ± 20.32 μmol/L vs. 75.34 ± 17.83 μmol/L, p < 0.05), the level of high-sensitive C-reactive protein (hs-CRP) was lower in group A than that in group B (2.38 ± 2.98 mg/L vs. 2.66 ± 3.24 mg/L, p < 0.05). The level of lipoprotein(a) [Lp(a)] was higher in group A than that in group B (68.35 ± 23.64 mg/L vs. 65.89 ± 21.87 mg/L, p < 0.05) and the average level of TC was lower in group A (3.84 ± 1.10 vs. 3.88 ± 1.09 mmol/L, p < 0.05). There was no significant difference in percentage of hypertension, current smoking and the average level of LDL-C between group A and group B (Table 1).

3.2. Comparison of constituent proportion of different kinds of statins applications in both groups

Importantly, we found that the constituent ratio of different kinds of statins application was significantly different between the two groups (p < 0.05), and the proportion of rosuvastatin application grew up in group B (20.00%) when compared with group A (10.50%, p < 0.05), the proportion of atorvastatin application kept stable and maintained the most majority in two groups (53.60% in group A, 51.10% in group B, Fig. 1)

3.3. Comparison of average dosage of statins applications in both groups

However, we found that the mean dosage of atorvastatin (18.56 ± 5.06 mg vs. 18.69 ± 6.55 mg) or rosuvastatin (10.34 ± 2.72 mg vs. 10.68 ± 4.06 mg) had no significant change between the two groups (Fig. 2).
3.4. Comparison of the situation of different intensity statins applications in both groups

The percentage of high-intensity statins was higher in group B than group A (2.9% in group B vs. 1.2% in group A, \( p = 0.0018 \)). Unfortunately, it was found that the average LDL-C level in each group was higher than 1.8 mmol/L (2.32 ± 0.84 mmol/L in group A vs. 2.35 ± 0.96 mmol/L in group B), the control rate of LDL-C (LDL-C < 1.8 mmol/L) in both groups was still very low, and no change was found about the situation of LDL-C level target achievement (< 1.8 mmol/L) after the announcement of 2013 ACC/AHA guideline (27.9% in group A vs. 26.9% in group B, \( p = 0.5077 \), Table 2).

3.5. Comparison of target achievement of LDL-C level in both groups

In both subgroups (subgroup A, \( n = 422 \); subgroup B, \( n = 550 \)) with LDL-C level target achievement (< 1.8 mmol/L) before and after the announcement of 2013 ACC/AHA guideline including age, gender, percentage of hypertension or dyslipidemia or DM, and the levels of ALT, AST, TBL, DBIL, GLU, Cr, BUN, hs-CRP, Lp(a), TC, TG, HDL-C and LDL-C were compared as shown in Table 2. The constitution proportion of different statins after the announcement of 2013 ACC/AHA guideline had significant difference when compared with that before the announcement of 2013 ACC/AHA guideline in details, the proportion of rosuvastatin application was higher than before (28.5% vs. 14.2%, \( p < 0.05 \), Fig. 4).

3.6. Comparison of constitution proportion of different statins in the subgroups with LDL-C level target achievement (< 1.8 mmol/L) before and after the announcement of 2013 ACC/AHA guideline

In both subgroups (subgroup A, \( n = 422 \); subgroup B, \( n = 550 \)) with LDL-C level target achievement (< 1.8 mmol/L), baseline characteristics including age, gender, percentage of hypertension or dyslipidemia or DM, and the levels of ALT, AST, TBL, DBIL, GLU, Cr, BUN, hs-CRP, Lp(a), TC, TG, HDL-C and LDL-C were compared as shown in Table 2. The constitution proportion of different statins after the announcement of 2013 ACC/AHA guideline had significant difference when compared with that before the announcement of 2013 ACC/AHA guideline. In details, the proportion of rosuvastatin application was higher than before (28.5% vs. 14.2%, \( p < 0.05 \), Fig. 4).

4. Discussion

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the American College of Cardiology (ACC) and the American...
Table 2

<table>
<thead>
<tr>
<th></th>
<th>Subgroup A</th>
<th>Subgroup B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years old</td>
<td>58.20 ± 10.41</td>
<td>58.40 ± 9.73</td>
<td>0.7583</td>
</tr>
<tr>
<td>Male (%)</td>
<td>337 (80.0%)</td>
<td>426 (77.5%)</td>
<td>0.3280</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>274 (65.4%)</td>
<td>346 (62.9%)</td>
<td>0.4244</td>
</tr>
<tr>
<td>Dyslipidemia (n, %)</td>
<td>328 (78.5%)</td>
<td>389 (70.9%)</td>
<td>0.0071*</td>
</tr>
<tr>
<td>DM (n, %)</td>
<td>126 (30.1%)</td>
<td>174 (31.6%)</td>
<td>0.6186</td>
</tr>
<tr>
<td>Current smoking (n, %)</td>
<td>242 (57.5%)</td>
<td>308 (56.0%)</td>
<td>0.6441</td>
</tr>
<tr>
<td>OMI (n, %)</td>
<td>308 (56.0%)</td>
<td>166 (30.7%)</td>
<td>0.9008</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>30.75 ± 30.70</td>
<td>28.93 ± 21.24</td>
<td>0.2982</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>20.41 ± 15.43</td>
<td>20.75 ± 8.61</td>
<td>0.6807</td>
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<tr>
<td>TRIL (μmol/L)</td>
<td>15.77 ± 5.60</td>
<td>14.92 ± 5.68</td>
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</tr>
<tr>
<td>DBIL (μmol/L)</td>
<td>4.06 ± 6.44</td>
<td>3.53 ± 5.92</td>
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<td>GLU (mmol/L)</td>
<td>5.65 ± 1.63</td>
<td>5.64 ± 1.50</td>
<td>0.9131</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td>76.11 ± 16.56</td>
<td>79.76 ± 22.22</td>
<td>0.0035*</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>5.79 ± 1.84</td>
<td>5.49 ± 1.56</td>
<td>0.0085*</td>
</tr>
<tr>
<td>HsCRP (mg/L)</td>
<td>2.46 ± 3.24</td>
<td>2.05 ± 2.78</td>
<td>0.0375</td>
</tr>
<tr>
<td>Lp(a) (mg/L)</td>
<td>63.24 ± 17.45</td>
<td>65.95 ± 19.31</td>
<td>0.0224*</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>66.32 ± 17.45</td>
<td>65.95 ± 19.31</td>
<td>0.0224*</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.62 ± 1.24</td>
<td>1.61 ± 1.32</td>
<td>0.8914</td>
</tr>
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<td>LDL-C (mmol/L)</td>
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Notes: DM, diabetes mellitus; OMI, old myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GLU, glucose; CR, creatinine; HsCRP, high-sensitivity C-reactive protein, Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. * Means p < 0.05.

Different kinds of statins including high-intensity, moderate-intensity and low-intensity statins were all available in the pharmacies of the five hospitals. The present study data suggested that after the announcement of 2013 ACC/AHA guideline, the usage of rosuvastatin became more, however, with no significant increase in dosage. The proportion of high-intensity statins application was increasing after the recommendation from the 2013 ACC/AHA guideline (2.9% vs. 1.2%, p < 0.05), but was still very low. Not surprisingly, no improvement in the proportion of target achievement of LDL-C level happened. Atorvastatin was still the most commonly prescribed for the patients with CAD, accounting for more than 50%. The prescription of rosuvastatin was increasing after the announcement of 2013 ACC/AHA guideline, suggesting that the cardiologists in China agreed with the recommendation of “high-intensity statin should be used in those patients with CAD” in some extent.

We previously reported a multiple-center data from China in 2011 [14], less than 70% and 40% of Chinese patients with CAD achieve the minimal LDL-C goal of <100 mg/dl and 70 mg/dl respectively, and more than 10% of patients had an elevated level of TG or decreased levels of HDL-C despite therapy. In DYSIS study published in 2014, Zhao et al. reported that low rate of target achievement of LDL-C in China [15], this cross-sectional trial included 25,697 patients treated with lipid-lowering agents from 122 centers between April 2012 and October 2012. Overall, 29.1% of patients had no lipid abnormalities, and 38.5% of patients did not achieve the therapeutic goal for LDL-C, either as a single lipid anomaly or associated with low HDL-C, elevated TG, or both. Subjects with low risk were more likely than those with very high and high risk to be at target LDL-C levels. Furthermore, 10.4% of very high-risk patients and 11.1% of high-risk patients who attained the LDL-C goal failed to attain non-HDL-C goals.

Our study showed that even after 2013 ACC/AHA guideline announcement, the rate of target achievement of LDL-C level in patients with CAD was still very low. The situation as mentioned above in China was not satisfying when comparing with that in western countries. In the study performed in United States recently, Tran NJ et al. [16], estimated the impact of the 2013 guideline on the pharmacy utilization of cholesterol-lowering medications in various risk groups in a managed care setting, they found that there would be a 25% increase in the proportion of the overall population that is treated with statins over the next 3 years, increasing from 3,909,407 (27.7%) patients to 4,892,668 (34.7%) patients. The largest proportion of the increase in statin utilization was projected to be for primary prevention in patients aged 40 to 75 years who were not receiving any cholesterol-lowering treatment at baseline. These projected changes would increase the overall number of statin prescriptions by 25% and will decrease the number of non-statin cholesterol-lowering medication prescriptions by 68% during the next 3 years. In addition, among the prospective cohort study of consecutive patients hospitalized for acute coronary syndrome (ACS) from 2009 to 2012 at four Swiss university hospitals [17], Gencer B et al. analyzed 1602 patients who survived one year after recruitment, 1578 (98%) patients were prescribed statin at discharge, with 1120 (70%) at high-intensity. 1507 patients (94%) reported taking statin at one year, with 909 (57%) at high-intensity. Among 482 patients discharged with sub-maximal statin, intensification of statin was only observed in 109 patients (23%). 773 (47%) patients reached the previous LDL-C targets, while 1014 (63%) reached the 2013 ACC/AHA guideline targets one year after ACS (p value < 0.001).

In our study, the dosage of statins used in those patients with CAD was compared before and after the announcement of 2013 ACC/AHA guideline. In this study, the average dosage of atorvastatin and rosuvastatin did not increase after the announcement of the guideline, neither atorvastatin nor rosuvastatin achieved the dosage of the recommendation in the guideline as high-intensity statins (atorvastatin 40-80 mg/day, rosuvastatin 20-40 mg/day). The average dosage changes of different statins before and after the announcement of the guideline were also compared in our study. The results showed that...
among the low and moderate-intensity statins, the dosage of simvastatin became lower than before, while the dosages of other statins including pravastatin, pitavastatin and lovastatin (Xuezhihikang) had no significant change after the announcement of the guideline. The dosage of fluvastatin was increasing due to the slow-releasing formulation with 80 mg per tablet replacing 40 mg per capsule as fast-releasing formulation.

As reported in our study, very low percentage (2.9%) of high-intensity statins were used in those patients with CAD even the recommendation of 2013 ACC/AHA guideline, suggesting that the cardiologists in the five hospitals were reluctant to prescribe high-intensity statins for very high-risk patients. Similarly, in the survey of Singapore, Sajita Setia et al. evaluated the impact of 2013 ACC/AHA guideline on the usage of statins in Asian countries, they found that although embracing the 2013 ACC/AHA guideline in clinical practice was expected to provide better clinical care to patients, high reluctance by physicians, especially in the use of high-dose statins [18]. Possible reasons for the reluctance of high-intensity statins usage were listed as following, the first one was that doctors and patients worried about potential side-effects of high-intensity statins, the second one was that some patients could not afford the fees of long-term high-intensity statins because no medical insurance covered in these patients, the third one was that some ethnic difference in the baseline level of LDL-C and response to statins between Asian and Western populations. In HPS2-THRIVE study, the rate of myopathy induced by statins in Chinese patients was about ten times than that in European patients [19]. Hence, more relative study is needed for this dilemma of cholesterol control in real world clinical practice.

There are some limitations in this study. Firstly, the sample size was not large enough. Secondly, the general characteristics between both the groups should be more matched to minimize the confounding factors. Thirdly, the study feature of cross-section with several center may not reflecting the whole situation in China with respect to the cholesterol management including statin use and LDL-C target achievement. A survey of large sample size with more centers may be needed in the future.

In summary, no much change of clinical practice with regard to cholesterol management was found in Chinese patients with CAD, accompanied by very low achievement of LDL-C target, suggesting that there is a great room for the improvement of cholesterol control in Chinese patients with CAD.

Conflict of interest

The authors have no conflict of interests.

Acknowledgments

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