Physicians' attitudes toward Lipid Management in Tertiary Hospitals in China

---A Cross-Sectional Study

by

Xiao Ji

Graduate Program in Global Health
Duke Kunshan University and Duke University

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Ann Marie Navar

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Henry Lynn

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Graduate Program
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ABSTRACT

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Abstract

Background: Hyperlipidemia is increasingly prevalent in China. Gaps are found between 2016 Chinese guideline for lipid management and other international guidelines. This study aims to identify attitudes and reported practice patterns for hyperlipidemia among Chinese physicians in tertiary hospitals. Methods: We collected data for 309 physicians on their adoption of guidelines, their attitudes of statin therapy and reported statin prescription patterns in four hypothetical patient scenarios (low risk/high LDL, high risk/high LDL, low risk/low LDL, and high risk/low LDL patients). Results: Overall, 63.75% of physicians adopted 2016 Chinese guideline. Most highly agreed with statins' effectiveness, but 57.94% concerned about the safety of high-intensity statins in the Chinese population. Physicians reported various LDL-C value for treatment target. In hypothetical scenarios, the prescription rate was highest for the high risk/high LDL patient (90.03%). Those who believed statins could prevent stroke and heart attack were more likely to prescribe statins (OR=5.67,p=0.002). The prescription rate was 81.42% for the patient at risk/low LDL. Those who believed statins could prolong life were more likely to prescribe (OR=2.51, P=0.009). Only 7.78% 2016 Chinese guideline adopters prescribed statins as guideline recommended on all four hypothetical patients. Most physicians (56.73%-73.91%) preferred moderate-intensity statins. Those who considered high-intensity statins shouldn't be routinely used in Chinese were less likely to prescribe

high-intensity statins(OR=0.33, p=0.004). Conclusions: Physicians concerned about statins' safety; We didn't find a specific practice pattern among physicians and guideline adopters' reported practices were not always concordant with the recommendations; Future studies are expected to focus on high-intensity statins and LDL-C target for treatment and training on guideline use is necessary;

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1. Introduction

1.1 The prevalence of hyperlipidemia in China

Hyperlipidemia is defined as elevations of fasting total cholesterol (TC) concentration that with or without elevated triglyceride (TG) concentration (Nelson, 2013). High blood lipid, especially high low-density lipoprotein (LDL-C), is well-documented pivotal risk factors for atherosclerosis cardiovascular disease (ASCVD) and coronary heart diseases (CHD) (Gordon, Castelli, & Hjortland, 1977; Nelson, 2013). In general, people with hyperlipidemia are about two times more risk on ASCVD (Mozaffarian, et al., 2016).

Data from World Health Organization recorded that the global prevalence of raised TC among adults (≥ 5.0 mmol/l) was 39% (37% for males and 40% for females) in 2008 (WHO, 2019). Many developed countries have been affected by dyslipidemia for decades. For example, over one third adults suffered from elevated LDL-C in the United States in 2011 (Centers for Disease Control and Prevention, 2011). The prevalence of dyslipidemia was between 34% to 50% in Spanish (Baena-Díez , et al., 2011; Guallar-Castillón , et al., 2012), 45.5% in Brazil (Lotufo, et al., 2016) and 64.5% in Italy (Marzetti, et al., 2018). As a developing country, China has a slightly lower prevalence of dyslipidemia than developed countries, it still poses a serious threat to the health of Chinese (Beaglehole, 2001). The most recent Chinese national survey between 2013 to 2014 implied that the prevalence of high TC, high LDL-C, high TG, and low high-density

lipoprotein cholesterol (HDL-C) was 6.9%, 8.1%, 13.8% and 20.4% respectively (Zhang, et al., 2018). A national representative sample proposed an increasing trend of dyslipidemia from 1980s and 2000–2001 (He, et al., 2004). Although the prevalence was slowing down recent years but the increasing incidence of hyperlipidemia in children and adolescents leads to a trend of younger age in dyslipidemia (Ding, Dong, & Mi, 2015). Besides, Stevens' study predicted that the number of CVD deaths would rise by 39 million in total between the 2016 and 2030 in China. "Preventative measures such as effective lipid and blood pressure management may reduce CVD burden substantially and provide large social value" (Stevens, et al., 2016).

1.2 Statin treatment for dyslipidemia

Statins are the most widely prescribed drugs to lower blood cholesterol and prevent CVDs (Ioannidis, 2014). They have been proofed effective in both primary and secondary preventions (Briel, Nordmann, & Bucher, 2005; Mills, E. J, et al., 2008; Taylor, Huffman, & Ebrahim, 2018; Hulten, Jackson, Douglas, George, & Villines, 2006). In China, the awareness, treatment, and control rate of dyslipidemia was estimated as low as 31.0%, 19.5% and 8.9% respectively(Pan, et al., 2016). Among those patients with high risk of CVD, only 5.5% were treated and up to 74.5% were uncontrolled with LDL-C (≥ 2.6 mmol/L) (Zhang, et al., 2018). The overall statin prescription rate on patients with CVDs was only 58.8% (from 2008 to 2014) which was lower than the 69.9% in the United States (from 2008 to 2012) (Huang, et al., 2017). However, still nearly half of adults at high

CVD risk (49.7%) were not receiving statins in the United States (Ueda, et al., 2018), and less than one-third patients with high risk were prescribed as a high-intensity dose (Salami, et al., 2017). Thus, under-treated statin therapy is problematic both domestically and internationally.

1.3 Domestic and international guidelines for lipid management

On the one hand, Chinese Joint committee enacted and updated guidelines for the management of dyslipidemia for Chinese population in decades; on the other hand, the American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) are at the forefront of improving clinical practice guidelines (CPGs) for CVD. They have a significant importance in Chinese clinical practice. It is estimated that more than half of are the Chinese versions of CPGs for CVD are published by the ACC, AHA, or ESC (Zhao & Hu, 2012). Currently, both domestic and international guidelines highlight statins as the firs line medication for lowering blood cholesterol and classify statins into low, medium, and high intensity doses. However, gaps are also found between domestic and international guidelines. (Tibrewala, Jivan, Oetgen, & Stone, 2018; Bartlomiejczyk, Penson, & Banach, 2019). Wu's research estimated an increased trend of rosuvastatin prescription from 10.5% to 20% in China ($p < 0.05$) two years after the establishment of the 2013 American Heart Association and American College of Cardiology (AHA/ACC) Guideline ("2013 AHA/ACC guideline" for short) and concluded an association between the increment and this guideline (Wu,

et al., 2017). In 2016, Chinese Journal of Cardiology renewed the 2007 Chinese guidelines on prevention and treatment of dyslipidemia in adults (Joint committee, 2007) and released the 2016 guideline ("2016 Chinese guideline" for short) (Joint committee, 2016). The main differences between 2016 Chinese guideline, 2013 AHA/ACC, and ESC guideline are demonstrated in Table 1.

Table 1: Comparison of 2016 Chinese guideline, 2013 ACC/AHA guideline and the ESC guideline.

	2016 Chinese guideline	***2013 ACC/AHA guideline***	***ESC guideline***
Evidence	Clinical and epidemiological studies on Chinese population	Only RCTs*, systematic reviews and meta-analysis	Both RCTs and observational studies
Outcome of Risk estimator	10-yr risk of coronary heart disease and ischemic stroke	10-yr risk of first hard ASCVD event (coronary heart disease death, nonfatal MI, or stroke)	10-yr risk of first fatal atherosclerotic event (MI, stroke, other Occlusive arterial disease, or sudden cardiac death)
LDL-C target for treatment	Very high risk: 1.8mmo/L High risk: 2.6mmol/L Low to middle risk: 3.4mmol/L	No target, treat according to underlying risk	Very high risk: 1.8mmol/L or a ≥50% reduction from baseline High risk: 2.5mmol/L Middle risk: 3mmol/L
High-intensity	Not recommended	75 yrs AND without contraindications or safety concerns: high-intensity statin >75 yrs OR with contraindications or safety concerns (irrespective of age):moderate-intensity statin	Maximally tolerated dose of statin to achieve target treatment goal
Initiation of drug treatment	No details, based on the target	Those who have ASCVD, with LDL-C ⩾ 190 mg/dl, and those with diabetes and elevated 10-year risk.	medium to high intensity statins to achieve the target goal.

*RCT: randomized control trials

First, they used different risk estimators. The 2016 Chinese guideline suggested using the risk of developing ischemic cardiovascular disease to calculate 10-year risk score but didn't give a specific equation for calculation (Joint committee, 2016). The 2013 AHA/ACC guideline adopted the Pooled Cohort Risk Equations to predict 10-year risk for a first hard ASCVD event (Stone, et al., 2014) and the ESC guideline employed the Systematic

Coronary Risk Evaluation (SCORE) estimator (Catapano , et al., 2016) . The 2016 Chinese guideline divided people into low-risk group, middle-risk group, high-risk group, and very high-risk group based on presence of hypertension, LDL-C level and other risk factors (smoking, low HDL-C, and age). This guideline also supplemented lifetime risk to identify patients under 55-year-old who need treatment. Second, similar to the ESC guideline, 2016 Chinese guideline insisted focusing on achieving a target LDL-C level for treatment. In contrast, 2013 AHA/ACC guidelines emphasized statin intensity dosing based on underlying risk. The recommended target LDL-C value was <1.8mmol/L, <2.6mmol/L, and <3.4mmol/L for very high-risk group, high-risk group, and low to middle-risk group respectively (Joint committee, 2016). Third, high-intensity statins were not recommended in Chinese guideline. On the contrary, both 2013 ACC/AHA guideline and the ESC guideline recommended starting with moderate to high-intensity statins for adults with high or very high ASCVD risk.

1.4 Impact of physicians' attitudes and significance of this study

Mainous et al. 's study denoted that the variation between physicians' attitudes toward prediabetes was significantly related to treatment and screening behaviors for diabetic preventions (Mainous, Tanner, Scuderi, Porter, & Carek, 2016). By this analogy, providers' attitudes could potentially affect their practice of statins. Worldwide, the use of lipid-lowering medication is controversial. On the one hand, many scholars claimed that statins were under-prescribed in strokes, transient ischemic attack (Turner, et al.,

2016), CVDs (Majeed , Moser , & Maxwell , 2000; Packham , et al., 1999; Fleetcroft, , Schofield, & Ashworth, 2014), fatty liver diseases (Del Ben, et al., 2017) and other relevant diseases. On the other hand, a lot of providers concern about severe side effects caused by statins and the over-prescription of statins, especially on elderly (Ruscica, et al., 2018). Controversy could be discovered among Chinese providers regarding treatment target, statin dosing, and statin related side effects (Li, et al., 2018; Zhao S. P., 2016).

What are Chinese physicians' attitudes and practice patterns of lipid lowering treatment? What and how do physicians in China follow the guidelines ? How well is the implementation of 2016 Chinese guideline after the announcement? These questions remain unanswered. Therefore, it is important to conduct this study to solve those questions with the data from the first-line health providers.

1.4 Aims

- Identify physicians' attitudes and practice patterns of lipid management at tertiary hospitals in China;
- Assess the agreement between reported prescription and 2016 Chinese guideline recommendations.
- Evaluate the factors associated with statin prescriptions.

2. Methods

This online self-administrated survey collected data for 309 physicians from 15 tertiary hospitals from multiple locations in China. Local collaborators distributed and delivered the questionnaire through WeChat, the most popular social software in China, and the major information collected included clinician's demographics, attitudes of statin therapy, and reported lipid management pattern. Data was analyzed using Stata 14 software. Categorical variables were presented by percentage and continuous variables were presented by medium. Using Chi- Square test of independence, differences of measures were tested statistically between 2016 Chinese guideline adopters and non-adopters, between statin prescribers and non-prescribers. Logistic regression was used to analyze association between various factors and stain prescriptions. This study was approved by Duke Kunshan University.

2.1 Setting

China is the fifth world largest country (CIA, 2018) and the most populous (above 1.404 billion) country in East Asia (Worldmeter, 2019) . It is also one of the most fastest developing country. China is divided into 4 ecological regions based on economic developments: northeastern, middle, eastern, and western regions. To achieve diversity and representativeness, we selected 1-2 locations in each region. Due to the limit of budget and resource, our study focused on tertiary hospitals.

2.2 Local collaborators and participants

After selecting the target locations, we used primary investigators' network to recruit local collaborators in each location. Cardiologists, endocrinologists or general practitioners who worked in tertiary hospitals and were willing to participate were recruited. Local collaborators then recruited cardiologists, endocrinologists, and general practitioners according to the inclusion criteria: 1) physicians who have achieved the certificate of medical practitioner qualification; 2) involved in lipid-lowering treatment decisions. Interns, students, and providers who has no experience on treating hyperlipidemia were excluded.

2.3 Procedures

2.3.1 Training of local collaborators

Prior to the initiation of this survey, the primary investigator provided a two-day training to collaborators through video teleconferences and messages. Specifically, the local collaborators were responsible for: 1) participating pilot test; 2) screening and recruiting local participants; 3) delivering the questionnaire via WeChat; 4) appropriately using budget based on the plan. Pilot study was conducted among 9 local collaborators, and the questionnaire was modified according to their comments.

2.3.2 Screening and recruitment of participants

Trained local collaborators used their resources to identify and screen eligible participants in their own department using with inclusion criteria. Thus, only the

physicians in our eligible hospitals could be screened. All potential participants were orally informed in person or by WeChat message and only those who gave an oral agreement were recruited.

2.4 Measures

2.4.1 Demographic information

We collected demographic information including gender, practice location (34 administrative regions for answer choices), specialty (cardiologist, endocrinologist, general practitioner, others), years in practice (1-5 years, 6-10 years, 11-20 years, over 20 years), and professional title (resident, attending, chief, and others). Physicians' specialties were divided into cardiologists and non-cardiologists. Their practice locations were categorized as Northern, Eastern, Western, and middle regions. See **Appendix A** for details of the questionnaire.

2.4.2 Reported guideline adoption

In our survey, we asked physicians to choose the guideline they primarily used to manage blood lipid. The answers were then classified into two sub-groups, Chinese guideline adopters and non-Chinese-guideline adopters("non-adopters" for short).

2.4.3 Reported statin prescription in hypothetical patient scenarios

We designed four primary prevention scenarios (Table 2). (1) Scenario A is a low-risk patient (2016 Chinese guideline) with an LDL-C of 4.3mmol/L. The estimated 10-year ASCVD risk score by ACC/AHA calculator and Framingham calculator was 2.4% and 4.8%

respectively. (2) Scenario B was an untreated hypertensive patient at high-risk(2016 Chinese guideline) with an elevated LDL-C (3.4mmol/L). The 10-year ASCVD risk calculated by ACC/AHA and Framingham calculators was 4.8% and 12.2%. (3) Scenario C was a low risk patient (2016 Chinese guideline) whose LDL-C was 2.8mmol/L and who had an elevated 10-year ASCVD risk score calculated by ACC/AHA (8.7%) and Framingham (8.8%) calculators, (4) Scenario D was a diabetic patient at high risk (2016 Chinese guideline) whose LDL-C was 2.3 mmol/L. The 10-year ASCVD risk score was also estimated high by ACC/AHA (9.7%) and Framingham (18.4%) calculators. Scenario A and B were highly recommended of statin therapy in the 2016 Chinese Guideline, but was optionally treated in 2013 AHA/ACC guideline. In contrast, patient C and D were highly recommended with moderate-high intensity statins in 2013 ACC/AHA guideline but was not strongly recommended in 2016 Chinese guideline due to the controlled LDL-C level. We asked participants to report the likelihood ("very unlikely", "unlikely", "neutral", "likely", and "very likely") to prescribe statins for each patient scenario (e.g. "How likely are you to recommend statin therapy"). The answers were further divided into statin prescribers and non-prescribers. Specifically, statin prescriber was defined as the physicians who answered likely or very likely, and non-prescriber referred to those who reported very unlikely, unlikely or neutral. Moreover, physicians who were likely or very likely to prescribe statins were led to a secondary question to choose statin dose from high, moderate, and low-intensity.

Table 2: Description of four hypothetical patient scenarios

Patient scenario	*Patient category*	*Characteristic*	*Comorbidities*	*Blood pressure (mmHg)*	*LDL (mmol/L)*	*ACC/AHA score (%)*	*Framingham score (%)*
A	Low risk/high LDL	40 y.o. female	Overweight	130/60	4.3	2.4	4.8
B	High risk/high LDL	45 y.o. male	Hypertension & obesity	150/110	3.4	4.8	12.2
C	Low risk/low LDL	70 y.o female	N/A	120/60	2.8	8.7	8.8
D	High risk/low LDL	51 y.o. male	Smoker & diabetes	120/60	2.3	9.7	18.4

We also designed a secondary prevention patient scenario who reported adherence to a high-intensity statin, yet persistently elevated LDL-C (3.4mmol/L). Participants were asked to select treatment plan from "no change", "change to a different statin", "add ezetimibe", "add fibrate", "add fish oil", and "add bile acid sequestrant". Answers were then divided into adding a non-statin lipid lowering treatment and not.

2.4.4 Reported LDL-C target for treatment

Whether to set treatment goals is one of the main differences between Chinese guideline and 2013 ACC/AHA guideline. In this questionnaire, we asked participants the LDL-C values for initiation of treatment and target LDL-C values for treatment (prior ASCVD patients and non-prior ASCVD patients). The answer options included no target, 30, 50, 70, 100, and 130 mg/dl.

2.4.5 Reported attitudes of statins' safety and efficacy

Our survey adopted and revised from Patient and Provider Assessment of Lipid Management (PALM) survey conducted by Navar et al in 2015 in the US (Navar, et al., 2017) . Physicians were asked to rate their agreement using a five-grade scale ("strongly

disagree", "disagree", "neither agree nor disagree", "agree", and "strongly agree") on the statements regarding statin safety (e.g. "I worry that the risks of statin therapy may be under-reported or under-appreciated"), and efficacy (e.g. "Statins are very effective in reducing risk of heart attack of stroke"). In addition to those questions, we supplemented two questions specifically focusing on Chinese population ("Chinese patients are more likely to experience statin related side effects", "high-intensity statins shouldn't be routinely used in Chinese"). Responses were divided into agreement group (agree, strongly agree) and disagreement groups(disagree, strongly disagree, neither agree nor disagree). We also measured the frequency of five major statin-related side effects (hepatic injury, muscle aches, weakness, diabetes, and memory loss) using a scale from "never", "rare", "occasionally", "often", to "frequently". Given the muscle aches condition caused by statins, frequency of different solutions (e.g. "reduce the statin dose", "reduce frequency") they adopted was scaled from "Almost Never", "sometimes", to "often".

This study protocol was approved by the institutional review board (IRB) of Duke Kushan University and supported by Duke Office of Information Technology (OIT) . The informed consent was placed at the first page of this online survey and participants could continue the survey by clicking "agree" button.

2.5. Analysis

Data derived from the survey questionnaires was entered a computerized spreadsheet (Microsoft Excel, Microsoft Office TM). All statistical analysis were

performed at the Duke Kunshan University using STATA MP 14.0. We initially collected 316 individual responses, among whom we excluded one who disagreed to participant and excluded six who completed less than 30%. Eventually, 309 responses were used for analyzing. The response rate was 74.53%. It was calculated via dividing the number of responses received by the number of questionnaires sent out. We also re-categorized the textual responses. For instance, clinician who put "cardiologist" in the textual blanket was grouped into cardiologist group. Answers of "associate chief physician" were grouped into "chief physician" to the question of "professional title". During data analysis process, categorical data was described using percentage or frequency. Chi-square test of independence was used to compare differences between categorical variables (Fisher's chi-square test was adopted when the individual frequency was less than 5), and $P<0.05$ was considered significant. Logistic regression model was used to evaluate different factors associated with reported statin prescription.

Specifically, there was four steps of analysis:

2.5.1. First, we described the sample according to demographic information, guideline adoption, attitudes of statins' safety/efficacy, frequency of statin related-side effects, frequency of solution to statin-related muscle aches, and target LDL-C for treatment. All variables were categorical and were presented by frequency.

2.5.2. Second, we compared the difference in demographic information, attitudes toward statins' safety/efficacy, frequency of statin related-side effects, and target LDL-C between 2016 guideline adopters and non-adopters.

2.5.3. Third, we estimated the proportion of physicians who were likely/very likely to prescribe statins for each hypothetical patient and the proportion of different dose advocates among statin prescribers. We then compared demographic information, guideline adoption, attitudes toward statins' safety/efficacy, frequency of statin related-side effects between statin prescribers and non-prescribers. Variables with a p-value smaller than 0.10 were furtherly recruited into the multi-variable logistic regression model to assess the association between different factors and statin prescription.

2.5.4. Last, using 4X4 tables, we measured and described the prescription patterns among physicians and evaluated the agreement between reported practice and 2016 Chinese guideline recommendations among Chinese guideline adopters.

3. Results

3.1 Demographics

This survey collected data for 309 physicians (243 cardiologists, 48 endocrinologists, 14 general practitioners, and 4 others) from 15 tertiary hospitals across China. Generally, this sample was dominated by female (n=196, 64.26%), attending physicians (n=145, 46.93%) and physicians with less than 10 years practice experience

(n=239, 77.35%). Geographically, physicians practiced in northeastern, eastern, western and middle region was 38.12%, 36.21%, 20.60% and 4.98% respectively.

3.2 Reported guideline adoption

Among 309 surveyed physicians, 197 (63.75%) reported following 2016 Chinese lipid guideline, 72 (23.30%) were primarily guided by ESC guideline, 28 (9.06%) by 2013 ACC/AHA guidelines, 3 (0.97%) by AACE guideline, 1 (0.32%) by IAS guideline, and 2 (0.65%) by others. Six participants (1.94%) didn't regularly use guideline (Figure 1)

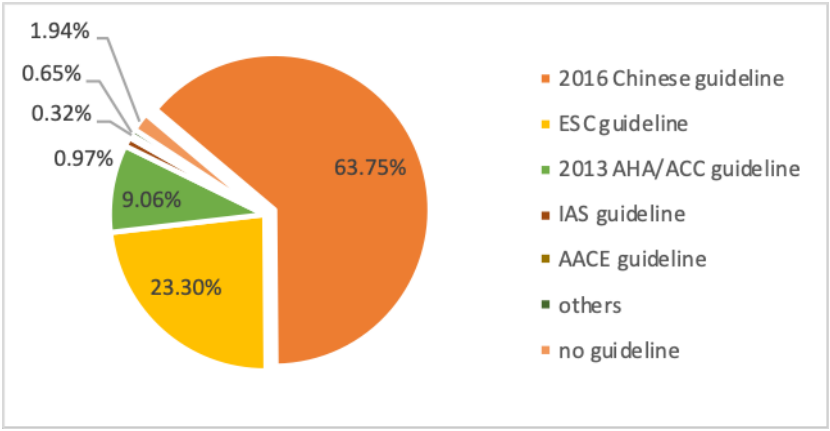

Figure 1: Proportion of different guideline adopters

3.3 Reported attitudes of statins' safety and efficacy

In this section, 288 physicians' responses were gathered (missing data was 6.80%) (Table 2). Generally, physicians reported a positive attitude toward statin's efficacy, but draw many concerns on statin's safety, especially in Chinses patient population. Specifically, 92.81% physicians believed in statins' effectiveness of reducing the risk of heart attack and stroke, and 60.56% physicians agreed/strongly agreed that statins could prolong life. Moreover, 29.76% of physicians believed that statins were unnecessary in

adults with already low LDL-C levels. Furthermore, 51.04% physicians agreed/strongly agreed that statins were extremely safe, yet 34.14% physicians hold a neutral attitude on statin's safety and many (41.32%) were worried by the statins' underestimated risk. Over half (57.94%) of physicians agreed/strongly agreed that high-intensity statin shouldn't be routinely used in Chinese population and 34.72% physicians believed that Chinese patients were more likely to experience statin-related side effects. Notably, many physicians hold a neutral attitude on those two statements (24.83% & 46.88%).

Table 3: Attitudes toward statin treatment, including safety and efficacy.

	Strongly disagree	*Disagree*	*Neutral*	*Agree*	*Strongly Agree*
Statin Safety					
Risk is underestimated, n(%)	2 (0.69%)	61(21.18%)	106 (36.81)	107(37.15)	12(4.17%)
High-intensity shouldn't be routinely used in Chinese, n(%)	5 (1.72%)	45(15.52%)	72 (24.83%)	140(48.28)	28(9.66%)
Statins are extremely safe, n(%)	7 (2.41%)	36(12.41%)	99 (34.14%)	126(43.45)	22(7.59%)
Chinese have more side effects, n(%)	3 (1.04%)	50(17.36%)	135(46.88)	93(32.29%)	7 (2.43%)
Statin Efficacy					
Effective in reducing heart attack and stroke, n(%)	0	3 (1.03%)	18 (6.16%)	139(47.60)	132(45.21%)
Unnecessary when LDL is low, n(%)	22 (7.61%)	123(42.56%)	58 (20.07%)	80(27.68%)	6 (2.08%)
Statins prolong life	5 (1.73%)	15 (5.19%)	94 (32.53%)	119(41.18)	56(19.38%)

3.4 Reported experience of statin-related side effects

We collected 290 responses in this section (missing data was 6.15%). In general, all five side effects were not considered that occurred frequently (1.37% to 7.24%). Hepatic injury was the most common side effect with 89.25% physicians reported it at least occasionally occurred when using statin treatment. Myalgias/muscle aches which was deemed as the most prevalent adverse event was considered occasionally happened by 48% physicians and rarely happened by 28.87% physicians. Similarly, 44.33% and 28.87%

of physicians considered weakness that rarely and occasionally happened respectively. Only 13% of physicians reported that they believed statins never cause memory loss, a side effect never shown to be associated with statins in randomized trials (Demasi, 2018). On the other hand, 14.5% of providers stated that statins never cause diabetes, a side effect that is known to be associated with statins (Freeman, et al., 2001; Downs, et al., 1998; Keech, et al., 2003). Details were presented in Figure 2.

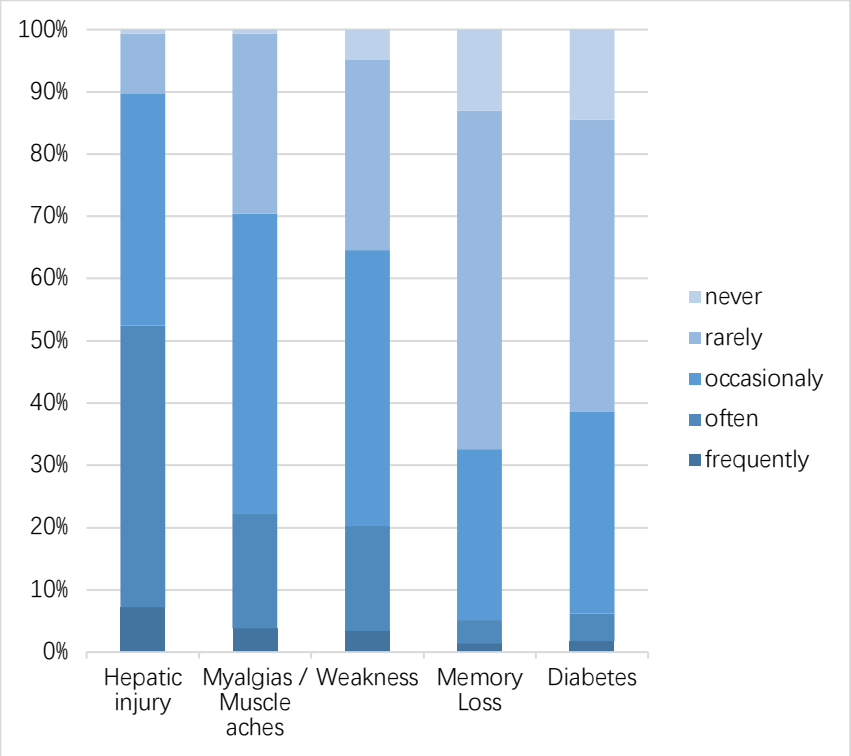

Figure 2: Frequency of statin-related side effects reported by physician.

Consistent with 2016 Chinese guideline recommendations, 67.71%, 46.69%, and 44.33% of physicians reported that they would often reduce statin's dosage , reduce activity, and stop statin respectively. Unexpectedly, as another recommended solution,

reducing frequency was often used by only 36.01% participants and 24.83% claimed that they never used it. Similarly, switching to another statin or non-statin therapy was never or only sometimes adopted by 76% and 84.37% physicians respectively. Besides, nearly half (45.10%) physicians never added Coenzyme Q as a supplementation (Figure 3).

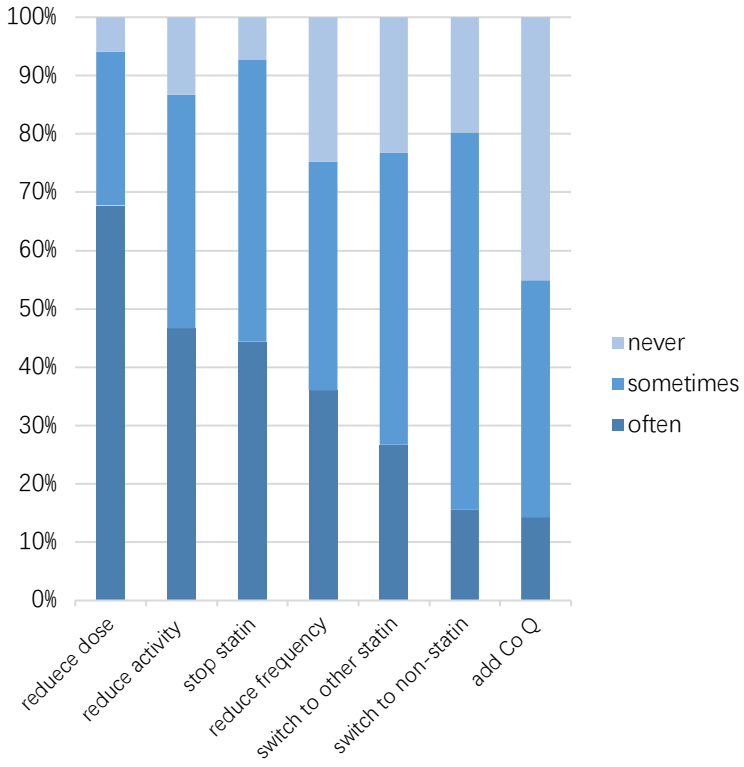

Figure 3: Frequency of solutions reported by physicians to address statin-related muscle aches

3.5 Reported LDL-C target for treatment

In general, 293 completed the questions in this section (missing data was 5.50%). The vast majority of physicians reported to use interventional target for patients with prior ASCVD (96.93%) and non-prior ASCVD/high risk (95.25%). However, the target values varied numerically. For the patients with prior-ASCVD, 46.76% physicians

reported a target LDL-C of 1.8mmol/L which was the recommendation in 2016 Chinese guideline, and 34.81% chose 2.6mmol/L. For the patients without prior-ASCVD but was at high risk, only 38.23% physicians would like to use the 2016 Chinese guideline recommended target LDL-C of 2.6mmol/L. Yet 34.13% and 10.92% of them preferred 1.8mmol/L and 3.4mmol/L respectively. Over half (50.85%) of them reported a higher LDL-C target than 2016 Chinese guideline recommendation. When selecting the threshold of medication therapy for prior-ASCVD patients, the answers exhibited significant variations among no target (24.57%), 1.8mmol/L (23.21%), 2.6mmol/L(33.79%), and 3.4(11.26%). Physicians tent to set a higher LDL-C target (36.52%) and threshold (45.05%) for the secondary prevention. Details were established in Figure 4. However, 2016 Chinese guideline adopters did not use the target LDL-C concordantly with the recommendations. The proportion of 2016 Chinese guideline adopters who reported usage of initiation LDL-C and treatment target for prior-ASCVD, and treatment target for non-prior-ASCVD as 2016 Chinese guideline recommended was only 20.97%, 43.55%, and 39.78% respectively (Table 4).

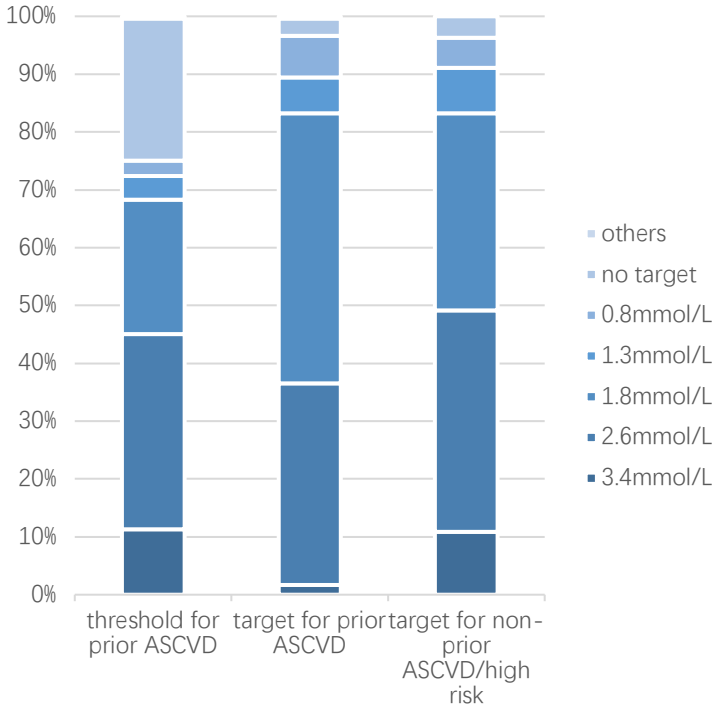

Figure 4: Proportion of different LDL-C target adoptions

3.6 Chinese guideline adopters vs. non-adopters

As shown in Table 4, the 2016 Chinese guideline adopters were more likely to use the recommended LDL-C target for high risk primary prevention(p=0.02). Guideline adopters were more positive with statins' safety (53.51% vs.46.57%) and effectiveness on prevention (94.65%vs.89.52%) and prolonging life (64.57% vs.59.62%). They were numerically less likely to use the recommended target and threshold for prior-ASCVD patients. They were more likely to add a non-statin medication for a secondary prevention patient with persistent high LDL-C (70.90%vs.61.11%). However, these differences above were not significant. More chief physicians was found in the guideline adopter group

compared with the non-adopter group (20.30% vs.15.18%). However, the difference was not statistically significant (p=0.61). There was no significant difference of characteristics including genders (p=0.80), specialties (p=0.16), and practice years (p=0.48), and office locations(p=0.63) between 2016 Chinese guideline adopters and non-adopters.

Table 4: Physician characteristics and attitudes of statins by 2016 Chinese guideline adopters vs. non-adopters

	Overall N=309	*Physician-reported adoption of 2016 Chinese guideline*		*P-value*
		Yes N= 197	*No N=112*	
Gender	305	193	112	
Male	109 (35.74%)	70 (36.27%)	39 (34.82%)	0.80
Female	196(64.26%)	123(63.73%)	73(65.18%)	
Specialty	309	197	112	
Cardiologist	243 (78.64%)	150 (76.14%)	93 (83.04%)	0.41
Endocrinologist	48(15.53%)	35(17.77%)	13(11.61%)	
General practitioner	14(4.53%)	10(5.08%)	4(35.40%)	
Others	4(1.29%)	2(1.02%)	2(1.79%)	
Years in practice	309	197	112	
0-5	151 (48.87%)	90 (45.69%)	61 (54.46%)	0.48
6-10	88 (28.48%)	58(29.44%)	30 (26.79%)	
11-20	47 (15.21%)	33(16.75%)	14 (12.50%)	
20+	23 (7.44%)	16 (8.12%)	7 (6.25%)	
Professional title	309	197	112	
Resident	103 (33.33%)	66 (33.50%)	37 (33.04%)	0.64
Attending	145 (46.93%)	88(44.67%)	57 (50.89%)	
Chief	57 (18.45%)	40 (20.30%)	17 (15.18%)	
Other	4 (1.29%)	3 (1.52%)	1 (0.89%)	
Office location	301	194	107	
Northeastern	115 (38.21%)	72 (37.11%)	43 (40.19%)	0.66
Middle	15 (4.98%)	12 (6.19%)	3 (2.80%)	
eastern	109 (36.21%)	70 (36.08%)	39 (36.45%)	
Western	62 (20.60%)	40 (20.62%)	22 (20.56%)	
Threshold for prior-ASCVD	293	186	107	
1.8mmol/L	68 (23.21%)	39 (20.97%)	29 (27.10%)	0.23
Others	225 (76.79%)	147 (79.38%)	78 (72.90%)	
Target for prior ASCVD	293	186	107	
1.8mmol/L	137 (46.76%)	81 (43.55%)	56 (52.34%)	0.15
Others	156 (52.24%)	105(56.45%)	51 (47.66%)	
Target for non-ASCVD/ high risk	293	186	107	
2.6mmol/L	102 (34.81%)	74 (39.78%)	28 (26.17%)	0.02

Others	191(65.19%)	112(60.22%)	79 (73.83%)	
Agreement on attitudes	288	184	104	
High-intensity shouldn't be routinely used in Chinese	168(57.93%)	106 (56.99%)	62 (59.62%)	0.66
Chinese are more vulnerable to side-effect	100(34.72%)	66 (35.68%)	34 (33.01%)	0.65
Statins are extremely safe	148(51.03%)	99(53.51%)	49(46.67%)	0.26
Risk is underestimated	119(41.32%)	83(45.11%)	36(34.62%)	0.08
Effective in reducing heart attack and stroke	271(92.81%)	177(94.65%)	94(89.52%)	0.10
Unnecessary when LDL is low	86(29.76%)	59(31.89%)	27(25.96%)	0.29
Statins prolong life	175(60.55%)	113(64.57%)	62(59.62%)	0.81
Addition of non-statin lipid-lowering treatment*	297	189	108	
High LDL-C despite adherence to high intensity statin	200 (67.34%)	134(70.90%)	66(61.11%)	0.08

* non-statin lipid lowering treatment include adding ezetimibe, fish oil, fibrate, and acid sequestrant.

3.7 Reported statin prescription patterns

In this section, 301 responses were collected with 2.6%-4.2% missing data. In the primary prevention patient scenarios (Figure 5), the prescription rate was high for the two patients with comorbidities/ high risk in 2016 Chinese guideline, but was relatively lower for the two patients at low risk in 2016 Chinese guideline. Most statin prescribers (from 56.73% to 75.00%) reported that they were likely to use a moderate-intensity statin on four patients. Specifically, the prescription rate was highest (90.03%) for the hypertensive patient with elevated LDL-C who had a ⩾10% (high risk group) risk estimate in Chinese guideline, but a <5% risk score calculated by ACC/AHA and Framingham calculators. The prescription rate was also high (81.42%) for the diabetic patient with controlled LDL-C whose risk was calculated ⩾10% (high risk group) in 2016 Chinese guideline and ⩾7% by ACC/AHA calculator and Framingham calculator. Contrarily, the prescription rate was lowest (34.55%) for the patient who had a < 5% risk score in 2016 Chinese guideline regardless the elevated LDL-C value and over 7% ACC/AHA and Framingham risk score

was high. Despite the low risk calculated by ACC/AHA and Framingham calculators and Chinese guideline calculator, the prescription rate was still 66% for the patient with uncontrolled LDL-C. However, the proportion of high-intensity statin supporters was significantly higher for the diabetic (24.48%) and hypertensive (14.23%) patients compared with other two patients (5.61% & 7.69%). Besides, for the patient with the lowest prescription rate, about one third of physicians reported a preference of low-intensity statins.

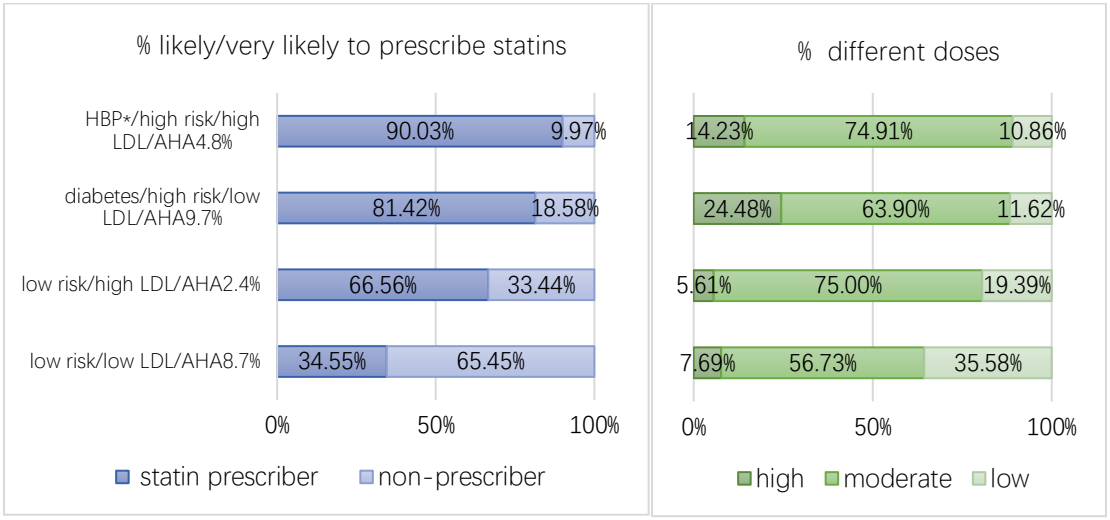

Figure 5: Proportion of statin prescribers and non-prescribers (left) in four scenarios; proportion of different doses of statins among statin prescribers (right).

*HBP: hypertension.

Figure 6 portrayed the responses to the secondary prevention patient with persistent high LDL-C value with a high-intensity statin therapy. Complying with 2016 Chinese guideline, 67.34% would like to add a non-statin lipid-lowering agent (ezetimibe, fibrate, fish oil, or bile acid sequestrant), 13% reported a switch to another statin, and 18.0% would not change treatment. Notably, over half (56.57%) of physicians reported a plan to

add Ezetimibe which was the primary non-statin medication recommended by 2016 Chinese guideline.

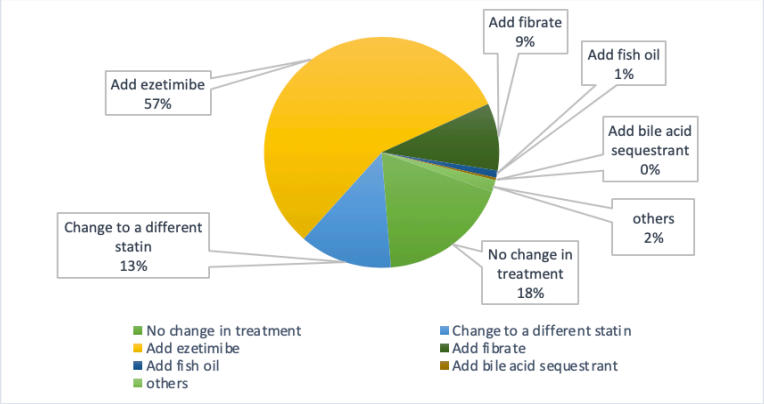

Figure 6: Proportion of different treatments for the secondary prevention patient with uncontrolled cholesterol.

3.8 Factors associated with statin prescription patterns

As shown in Table 5 and Table 7, no significant difference of characteristics including gender, specialty, years in practice and location was identified in statin prescribers versus non-prescribers, and in high-intensity prescribers versus low-and-moderate-intensity prescribers. Individual regression models Included significant variables ($p<0.10$) from chi-square tests, as well as the factors could potentially affect statin prescription (gender, years in practice, and specialty).

Table 5: Characteristics and attitudes of statins by statin prescription on four hypothetical patients.

	likely/very likely to prescribe statins											
	Low risk/high LDL		*p*	*High risk/high LDL*		*p*	*Low risk/low LDL*		*P*	*High risk/low LDL*		*p*
	Yes	*No*		*Yes*	*No*		*Yes*	*No*		*Yes*	*No*	
Male	73 (37.24%)	33(33.33%)	0.51	100(37.31)	7(24.14%)	0.16	42(40.38%)	65(33.68%)	0.25	80 (33.76%)	26(47.27%)	0.06
Cardiologist	156(78.39%)	79(79.00%)	0.90	216(79.70)	21(70.00%)	0.22	77(70.38%)	161(81.73%)	0.12	195(80.91%)	39(70.91%)	0.10
Practice years												
0-5	103(51.76%)	45(45.00%)	0.37	132(48.71)	16(53.33%)	0.80	50(48.77%)	98(49.75%)	0.57	114(47.30%)	31(53.36%)	0.45
6-10	55 (27.64%)	28(28.00%)		76(28.04%)	9(30.00%)		34(32.69%)	51(25.89%)		69 (28.63%)	16(29.09%)	
11-20	25 (12.56%)	20(20.00%)		41(15.13%)	4(13.33%)		14(13.46%)	32(16.24%)		39(16.18%)	5(9.09%)	
20+	16 (8.04%)	7(7.00%)		22(8.12%)	1(3.33%)		6(5.77%)	16(8.12%)		19(7.88%)	3(5.45%)	
Location, n(%)												
Northeastern	67 (34.90%)	43(43.43%)	0.48	97(36.74%)	14(48.28%)	0.21	32(32.00%)	79(40.93%)	0.24	89(37.87%)	21(61.76%)	0.17
Middle	10 (52.08%)	5(5.05%)		15(5.68%)	0(0.00%)		5(5.00%)	10(5.18%)		9(3.83%)	6(17.65%)	
Eastern	76(39.58%)	31(31.31%)		99(37.50%)	7(24.14%)		36(36.00%)	70(36.27%)		88(37.45%)	17(31.48%)	
Western	39(20.31%)	20(20.20%)		53(20.08%)	8(27.59%)		27(27.00%)	34(17.62%)		49(20.85%)	10(18.52%)	
2016 Guideline adoption	133(66.83%)	56(56.00%)	0.07	172(63.47%)	19(63.33%)	0.99	64(61.54%)	128(64.97%)	0.56	156(64.73%)	33(60.00%)	0.51
Agreement on attitudes of statins												
Risk is underestimated	83(44.39%)	34(34.69%)	0.11	108(42.02%)	10(33.33%)	0.36	47(47.47%)	72(38.10%)	0.13	98(42.24%)	21(39.62%)	0.72
High-intensity shouldn't be routinely used in Chinese	102(54.26%)	63(63.64%)	0.13	152(58.69%)	15(50.00%)	0.36	58(58.59%)	110(57.59%)	0.87	136(58.37%)	30(55.56%)	0.71
Chinese are more vulnerable to side-effect	68(36.56%)	31(31.31%)	0.38	89(34.63%)	10(33.33%)	0.89	35(35.71%)	65(34.21%)	0.80	89(38.53%)	11(20.37%)	0.01
Statins are extremely safe	98(52.13%)	47(47.96%)	0.50	131(50.78%)	15(50.00%)	0.94	48(48.00%)	100(52.63%)	0.45	124(53.45%)	22(40.74%)	0.092
Effective in reducing heart attack and stroke	178(94.68%)	89(89.00%)	0.08	246(94.62%)	23(76.67%)	0.00	94(94.00%)	177(92.19%)	0.57	220(94.42%)	48(87.27%)	0.06
Statins could prolong life	117(62.57%)	56(56.57%)	0.32	155(60.08%)	19(63.33%)	0.73	64(65.31%)	111(58.16%)	0.24	151(65.09%)	24(44.44%)	0.005
Unnecessary for low LDL	51(27.27%)	33(33.33%)	0.28	76(29.46%)	9(30.00%)	0.95	27(27.55%)	59(30.89%)	0.56	63(27.16%)	21(38.89%)	0.09
Frequent/often side effects												
Myalgias	47(24.74%)	17(17.35%)	0.15	58(22.31%)	6(20.00%)	0.77	33(33.00%)	32(16.75%)	0.002	51(21.79%)	13(24.07%)	0.72
Hepatic injury	102(53.97%)	49(50.00%)	0.52	139(53.67%)	12(40.00%)	0.16	58(58.59%)	94(49.21%)	0.13	123(52.79%)	29(53.70%)	0.90
Memory Loss	9(4.74%)	5(5.10%)	0.89	12(4.62%)	2(6.67%)	0.65	10(10.00%)	5(2.62%)	0.007	12(5.13%)	3(5.56%)	1.00
Diabetes	12(6.35%)	5(5.10%)	0.67	14(5.41%)	3(10.00%)	0.40	7(7.07%)	11(5.76%)	0.66	15(6.44%)	3(5.56%)	1.00
Weaknes	43(22.75%)	15(15.31%)	0.14	50(19.31%)	8(26.67%)	0.34	20(20.00%)	39(20.42%)	0.93	50 (21.46%)	9(16.67%)	0.43

Table 6: Factors associated with statin prescription in different hypothetical patient scenarios *

	OR	*95% CI*	*p*
Low risk/high LDL			
Years in practice			
0-5	1		
6-10	0.82	0.45,1.49	0.522
11-20	0.48	0.24,0.99	0.046
20+	0.91	0.34,2.44	0.86
High risk/high LDL			
Believe in statin's effectiveness	5.67	1,94, 16.52	0.002
Low risk/low LDL			
Frequent muscle aches	2.12	1.16, 3.87	0.014
High risk/low LDL			
Female	2.71	1.37, 5.36	0.004
Believe that statins prolong life	2.51	1.25, 5.04	0.009
Chinese are more vulnerable to side effects	2.50	1.13, 5.55	0.024
Statins are unnecessary for low LDL	0.49	0.24,0.97	0.004

*Multivariable models include significant results (p<1.0) and adjustment of gender, guideline adoption, specialty and years in practice, only significant results are listed.

We found that 1) The proportion of physicians who believed in statins' effectiveness in reducing heart attack and stroke were statistically higher in statin prescriber group for the patient with high LDL/low risk in Chinese guideline (p<0.001). However, this association was not significant in regression model (Table 5). Compared with physicians who had a 0-5 years practice, those who had a 11-20-year experience were less likely to prescribe statins on this patient (OR=0.48, CI 0.24,0.99, p=0.046). However, the association was not statistically strong (Table 6). No further factor was identified associated with the prescription of high-intensity statins among statin prescribers for this patient either. 2) In the high LDL-C/high risk in Chinese guideline patient scenario, the statin prescribers were more likely to believe in statins' effectiveness in preventing stroke and heart attack(p=0.00). This association persisted in the regression model(OR=5.67, CI 1.94,16.52,

Table 7: Characteristics and attitudes of statins by high-intensity statin prescription on four hypothetical patients.

	high-intensity statins prescription										
	Low risk/high LDL		***p***	***High risk/high LDL***		***p***	***Low risk/low LDL***		***p***	***High risk/low LDL***		***p***
	Yes	***No***		***Yes***	***No***		***Yes***	***No***		***Yes***	***No***	
Male	5(45.45%)	68(37.36%)	0.59	17(44.74%)	81(35.84%)	0.29	6(75%)	36(37.5%)	0.059	24(42.11%)	56(31.11%)	0.13
Cardiologist	2 (0.18%)	144(77.84%)	1.00	28(73.68%)	185(80.79%)	0.31	5(62.5%)	72(75%)	0.43	52(88.14%)	143(78.57%)	0.10
Practice years												
0-5	6(54.55%)	96(51.89%)	0.38	23(60.53%)	108(47.16%)	0.10	5(62.50%)	45(46.88%)	0.93	27(45.76%)	87(47.80%)	0.96
6-10	2(18.18%)	53(28.65%)		5(13.16%)	69(30.13%)		2(25.00%)	32(33.33%)		18(30.51%)	51(28.02%)	
11-20	3(27.27%)	21(11.35%)		8(21.53%)	33(14.41%)		1(12.50%)	13(13.54%)		10(16.95%)	29(15.93%)	
20+	0 (0%)	15(8.11%)		2(5.26%)	19(8.30%)		(0%)	6(6.25%)		4(6.78%)	15(8.24%)	
Location, n(%)												
Northeastern	3(37.50%)	64(35.36%)	0.62	14(40.00%)	81(36%)	0.91	1(14.29%)	31(33.33%)	0.42	21(37.50%)	68(37.99%)	0.89
Middle	0 (0%)	10(6.21%)		1(2.86%)	14(6.22%)		1(14.29%)	4(4.30%)		3(5.36%)	6(3.35%)	
Eastern	2(25.00%)	72(39.78%)		14(40.00%)	84(37.33%)		3(42.86%)	33(35.48%)		20(35.71%)	68(37.99%)	
Western	3(37.50%)	35(19.34%)		6(17.14%)	46(20.44%)		2(28.57%)	25(26.88%)		12(21.43%)	37(20.67%)	
2016 Guideline adoption	6(54.55%)	126(68.11%)	0.35	26(68.42%)	144(62.88%)	0.51	8(100%)	56(58.33%)	0.022	44(74.58%)	112(61.54%)	0.069
Agreement of attitudes												
Risk is underestimated	2(22.22%)	81(45.76%)	0.30	19(51.35%)	88(40.55%)	0.22	5(62.50%)	42(46.15%)	0.47	25(46.30%)	73(41.01%)	0.49
High-intensity shouldn't be routinely used in Chinese	4(44.44%)	98(56%)	0.73	14(37.84%)	138(63.01%)	0.004	6(75.00%)	52(57.14%)	0.46	27(50.00%)	109(60.89%)	0.16
Chinese are more vulnerable to side-effect	0(0%)	68(38.42%)	0.028	12(33.33%)	77(35.32%)	0.82	4(57.14%)	31(34.07%)	0.24	26(49.06%)	63(35.39%)	0.07
Statins are extremely safe	5(55.56%)	92(51.69%)	1.00	20(57.14%)	110(50%)	0.43	2(28.57%)	46(49.46%)	0.44	30(54.54%)	94(53.11%)	0.88
Effective in reducing heart attack and stroke	8(100%)	169(94.41%)	1.00	36(100%)	208(94.12%)	0.23	6(85.71%)	88(94.62%)	0.36	52(96.30%)	168(93.85%)	0.74
Statins could prolong life	5(62.5%)	111(62.36%)	1.00	24(66.67%)	129(58.90%)	0.38	5(71.43%)	59(64.84%)	1.00	34(64.15%)	117(65.36%)	0.87
Unnecessary for low LDL	2(25%)	49(27.53%)	1.00	6(16.67%)	j	0.07	3(42.86%)	24(26.37%)	0.39	14(26.42%)	49(27.37%)	0.89
Frequent/often side effects												
Myalgias	2(22.22%)	45(25%)	1.00	8(21.62%)	49(22.27%)	0.93	4(57.14%)	29(31.18%)	0.21	18(31.58%)	33(18.64%)	0.04
Hepatic injury	5(62.50%)	97(53.89%)	0.73	23(62.16%)	114(52.05%)	0.25	6(85.71%)	52(56.52%)	0.23	35(62.50%)	88(49.72%)	0.10
Memory Loss	1(11.11%)	8(4.44%)	0.36	2(5.26%)	9(4.11%)	0.67	4(50.00%)	6(6.52%)	0.003	6(10.53%)	6(3.39%)	0.034
Diabetes	0(0%)	12(6.67%)	1.00	4(10.81%)	10(4.57%)	0.13	2(28.57%)	5(5.43%)	0.076	4(7.14%)	11(6.21%)	0.76
Weakness	3(37.50%)	40(22.22%)	0.39	7(18.92%)	43(19.63%)	0.92	4(57.14%)	16(17.20%)	0.028	17(30.56%)	33(18.64%)	0.063

p=0.002) (Table 6). Among those statin prescribers, those who believed that high-intensity statins should not be routinely used in Chinese were less likely to prescribe high-intensity statins (p=0.04) (Table 7). This association was persistently observed in the result of regression model (OR=0.33, CI 0.57,0.70, P=0.004) (Table 8). Besides, physicians who had a 6-10-year practice experience were less likely to prescribe high-intensity statins for this patient compared with those had a 0-5 years (OR=0.33, CI 0.13, 1.02, p=0.039). 3) Statin prescribers for the patient with low LDL-C/ low risk in Chinese guideline were more likely to report a frequent experience of myalgias (p=0.02) and memory loss (p=0.007) (Table 5). However, only the association between frequent muscle aches and statin prescriptions was found in our regression model (OR=2.12, CI 1.61,3.87, p=0.014) (Table 6). High-intensity statin prescribers in this scenario were more likely to be 2016 guideline adopters (p=0.022), to be those who frequently experienced memory loss (p=0.03) and weakness side effects (p=0.028) (Table 7). However, those associations were not significant in the regression model. 4) For the patient with low LDL/high risk in Chinese guideline, compared with non-statin prescribers, statin prescribes were more likely to be those who believed that statins could prolong life (p=0.005) and those who believed that Chinese were more vulnerable to side effects (p=0.01) (Table 5). These associations could also be detected in the regression model respectively (OR=2.51, CI 1.25, 5.04, p=0.009 & OR=2.50, CI 1.13,5.55, p=0.024) (Table 6). Moreover, females (0R=2.71 CI 1.37,5.36, p=0.004) were more likely to

prescribe statins, but those who believed that statins were not necessary for patients with low LDL-C were less likely to report a prescription (OR=0.49, CI 0.24,0.97, p=0.004) (**Table 6**). More physicians who reported frequent experience of muscle aches (p=0.04)and memory loss (p=0.034) were discovered among high-intensity statin prescribers (**Table 7**). Nevertheless, no such association was found in the regression model. Unexpectedly, 2016 guideline adopters were more likely to prescribe high-intensity statins for this patient who was not recommended by the Chinese guideline (OR=2.15 CI 1.03, 4.51, P=0.04) (**Table 8**).

Table 8: Factors associated with high-intensity statin prescription in different hypothetical patient scenarios

	OR	*95% CI*	*p*
High risk/high LDL			
High-intensity shouldn't be routinely used in Chinese	0.33	0.57, 0.70	0.004
Years in practice			
0-5	1		
6-10	0.33	0.13-1.02	0.039
11-20	1.18	0.46-3.03	0.74
20+	0.61	0.13-2.94	0.54
High risk/low LDL			
2016 guideline adoption	2.15	1.03, 4.51	0.043

*Multivariable models include significant results (p<1.0) and adjustment of gender, guideline adoption, specialty and years in practice, only significant results are listed.

3.6 Reported prescription vs. guideline recommendations

Among all participants, 23.63% of them reported statin prescription on all four hypothetical patients and 1.71% of them reported not to use statins for all patients (Table 9). Specifically, a large proportion (73.98%) of participants reported prescription for both the hypertensive (B) and diabetic (D) patients. Many (60.96%) reported to use statins for

both patients (A&B) with uncontrolled LDL-C, and 31.85% reported to prescribe statins for both patients with high ACC/AHA risk score (C&D). Only 16.44% of them reported not to treat statins for both two patients with controlled LDL-C (C&D). Generally, only 7.88% of them treated all four patients as 2016 Chinese guideline recommended, and 1.03% followed the recommendations in ACC/AHA guideline.

Similarly, only 8% of guideline adopters chose to prescribe statins for all four hypothetical patients as 2016 guideline recommended (Table 9-10). Specifically, 65.05% of them claimed that they would use statins for the two patients with uncontrolled LDL-C(A&B) recommended by 2016 Chinese guideline, and 15.59% of them reported a preference not to use statins for the two patients with controlled LDL-C (C&D) who were not highly recommended by 2016 Chinese guideline.

Table 9: Agreement of physicians' reported prescription for four scenarios

				Low risk/high LDL patient				
				No		*Yes*		*Total*
				High risk/high LDL		*High risk/high LDL*		
				No	*Yes*	*No*	*Yes*	
High risk/low LDL	*No*	*Low risk/low LDL*	*No*	5(1.71%)	17(5.82%)	3(1.03%)	23(7.88%)	48(16.44%)
			Yes	0(0%)	1(0.34%)	0(0%)	5(1.71%)	6(2.05%)
	Yes	*Low risk/low LDL*	*No*	8(2.74)	47(16.10%)	9(3.08%)	81(27.74%)	145(49.66%)
			Yes	3(1.03%)	19(6.51%)	2(0.68%)	69(23.63%)	93(31.85%)
Total				16(5.48%)	84(28.77%)	14(4.78%(	178(60.96%)	292

Table 10: Agreement of 2016 Chinese guideline adopters' reported prescription for four scenarios

				Low risk/high LDL patient				*Total*
				No *High risk/high LDL*		*Yes* *High risk/high LDL*		
				No	*Yes*	*No*	*Yes*	
High risk/low	*No*	*Low risk/low*	*No*	3(1.61%)	8(4.30%)	3(1.61%)	15(8.06%)	29(15.59%)
LDL		*LDL*	*Yes*	0(0%)	1(0.54%)	0(0%)	2(1.08%)	3(1.61%)
	Yes	*Low risk/low*	*No*	5(2.69%)	30(16.13%)	4(2.15%)	57(30.65%)	96(51.62%)
		LDL	*Yes*	2(1.08%)	7(3.76%)	2(1.08%)	47(25.27%)	58(31.18%)
	Total			10(5.38%)	46(24.73%)	9(4.84%)	121(65.05%)	186

4. Discussion

4.1. Summary of study results

In this analysis, we measured physicians' attitudes of statin therapy and their reported statin prescription patterns. The results demonstrated: 1) Physicians at tertiary hospitals mainly followed 2016 Chinese guideline; 2) Physicians reported a general positive attitudes on statins' efficacy, but had concerns about statins' safety; 3) Most physicians reported to set a target LDL-C for treatment but the values varied; 4) The reported prescription rate was high for two patients at high risk in Chinese guideline (hypertension and diabetes) regardless LDL-C level, but very limited physicians reported prescription as 2016 Chinese guideline or ACC/AHA guideline recommended; 5) Chinese guideline adopters' practice pattern did not always align with 2016 Chinese guideline recommendations either; 6) Most physicians preferred moderate-intensity statins; 7) physicians' attitudes and their experience of side effects were associated with their reported prescriptions.

4.2. The critical role of Chinese guideline

Not surprisingly, 2016 Chinese guideline was the major guideline physician primarily followed (63.75%).The ESC guideline was also commonly used (23.30%). Unexpectedly, 2013 AHA/ACC guideline was adopted by only 9.06% of physicians. Given the low adoption rate of ACC/AHA guideline and the small proportion of high-intensity statin prescription rate in our study, we argue that the influence of 2013 ACC/AHA

guideline on statin application in China measured in Wu's study that was questionable (Wu, et al., 2017). Instead, 2016 Chinese guideline plays a more critical role and calls for more evaluation.

4.3. Concerns about statin safety in Chinese

It has been well confirmed that statins are effective to prevent ASCVD and stroke (Amarenco , Bogousslavsky , & Callahan, 2006; Shepherd, Blauw , & Murphy, 2002; Colhoun , Betteridge, & Durrington , 2004; Furberg, et al., 2002; Wilt, et al., 2004). Statins' importance was highlighted in all lipid management guidelines. Consistent with guidelines and evidence-based recommendations, our study also demonstrated a high level of physician acceptance of statin effectiveness in reducing stroke and heart attack (92.8%) and in prolonging life (60.65%). Our participants also showed a great concern about statins' safety, especially about the safety of high-intensity statins in Chinese population which was also consistent with the claim presented in 2016 Chinese guideline. This also confirmed the importance of Chinese guideline among Chinese physicians at tertiary hospitals. The concerns may also be related with their frequent experiences of statin-related side effects. However, among five common side effects we provided in the survey, none of them was considered that happened frequently. It has been proved that statin-related hepatic injury and muscle aches were more likely to occur in Chinese population compared with the Europeans (HPS2-THRIVE Collaborative Group. , 2013). From this, we may imply that hepatic injury and muscle aches were the major concerns

among Chinese physicians. This was also reflected in our study that hepatic injury and muscle aches were the most common side effects reported by physicians. Recently, increasing evidence showed that stains were associated with new-onsite diabetes. However, about 60% of our participants considered statin-related diabetes never or rarely happened. As the most controversial side effect, memory loss was also deemed as the side effect rarely happened by most participants. Yet, it presented a compliance with the results of previous randomized control trails (RCTs) which failed to find statistical association between statins and memory loss. More observational studies and RCTs are needed to better understand the impact of clinical statin-related side effects.

4.4. Reported controversial treatment targets

Although treatment targets for each risk group were clearly indicated in 2016 Chinese guideline, there was no clear description of when to initiate drug therapy. Majorly the initiation of therapy depended on the LDL-C value and the recommended target. This may account for the significant difference we found in LDL-C threshold values for treatment reported by our participants. A further explicit explanation should be supplemented into 2016 Chinese guideline in the future. Moreover, only limited proportions of guideline adopters (20.97%-43.55%) reported use of treatment targets as recommended by 2016 guideline in three scenarios. The change of LDL-C treatment in 2016 Chinese may be one of the reasons. According to statistical evidence (Verma, Fernandez, & Saucier, 2018; LaRosa, et al., 2005), the treatment target LDL-C for secondary

prevention was lowered from 2.0mmol/L in 2007 Chinese guideline (Joint committee, 2007) to 1.8mmol/L in 2016 Chinese guideline (Joint committee, 2016). Many professionals disputed over this change (Zhao, 2016). This disagreement could be seen in our results that many physicians used higher target LDL-C than 2016 Chinese guideline recommendation. This may explain the very low LDL control rate of 26.9%(<1.8mmol/L) for secondary prevention in Chinese patients (Wu N. Q., et al., 2017). In other words, the subjective higher treatment targets set by physicians may contribute to the constantly increased CVD incidence and uncontrolled LDL-C. This may also reveal a poor understanding of 2016 guideline and a better training may potentially address the problems.

4.5. Reported prescription for primary prevention

In our analysis, we did not find a clear prescription pattern among physicians for primary prevention patients. This may reflect the complex influence of various guidelines on physicians' practices and the poor implementation of 2016 Chinese guidelines. Only about 1% of physicians prescribed on four patients following 2013 ACC/AHA guideline which furtherly confirmed our doubt on its impact. 1) As expected, the patient with comorbidities (hypertension & smoking) and significantly elevated LDL-C had the highest statin prescription rate regardless the low ACC/AHA risk score. Physicians' belief in statins' effectiveness were significantly associated with their prescription which indicated that enhancing training of statins' effectiveness could

potentially optimize the lipid management. 2) In contrast, the patient with a controlled LDL-C and was estimated as low risk in Chinese guideline had the lowest prescription regardless the high ACC/AHA risk score (>7%). This may indicate that ACC/AHA risk calculation was not highly valued among Chinese physicians. The frequent experience of muscle aches was related to physicians' prescription for this low LDL-C/low risk patient in both Chi square test and regression test. This may be interpreted that physicians who were more likely to prescribe for the patient not recommended by 2016 Chinese guideline might be more positive in using statins. Therefore, they could be more likely to face to side effects. 3) The prescription rate was also high for the patient with diabetes/high risk, though the LDL-C was lower than recommended target in 2016 Chinese guideline. The high prescription rate may be the result from physicians' belief on statins' effectiveness in prolonging life. Female was associated with the prescription for the diabetic patient, it may be a result from the larger proportion of female participants in our sample. More data is required to confirm the association between gender and statin prescription. We also found that physicians who believed Chinese were more vulnerable to side effects were more likely to prescribe statins for the diabetic patient. We did not find evidence to support this. We considered that since this is a cross-sectional study, the association we measured may be adverse. This means that the physicians who were more likely to prescribe statins might have more experience of side effects. Therefore, they might produce a belief that Chinese were more likely to experience side effects. Moreover, high

prescription rate for the patient with a controlled LDL-C might be a reflection to the result we found that over half of physicians reported a lower LDL-C target for primary prevention patients at high risk and statin prescribers' inclination to believe that stains were necessary for patients with low LDL-C. Besides, physicians may pay more attention on patients' comorbidities.

4.6. Discordance between prescription and recommendations

Despite the high adoption rate of 2016 Chinese guideline, adopters' reported statin prescription pattern was not always concordant with the recommendations. The proportion of physicians who reported to prescribe statins on all four patients as recommended in 2016 Chinese guideline was fairly small. Again, this reflected a poor understanding and implementation of this guideline. The main disagreement lied on the treatment for the diabetic patient at high risk/low LDL and the patient at low risk/high LDL-C. This responded to the variation of LDL-C targets and may also reveal a poor understanding of the risk stratification used in 2016 Chinese guideline. More training on those two parts is essentially requisite. We found that the positive attitudes of statins' safety and efficacy could predict their prescription of statins which may predict a crucial role of the training to change physicians' attitudes. Interestingly, females were more likely to prescribe statins for the patient with diabetes, at high risk with low LDL which may be caused by the gender disproportionality of our sample. Besides, since this is a cross-sectional study, when we interpret the causal relationship, the direction may be adverse

(e.g. physicians who had frequent experience of muscle aches and who had a belief that Chinese were more likely to suffer side effects were more likely to prescribe statins). Chinese Further observational study or RCT are needed to confirm the associations.

Studies in China and abroad have confirmed that high-dose statins reduced the risk of ASCVD events better than moderate-dose statins (Zhao, 2016; Cannon, Steinberg, , Murphy, Mega, & Braunwald, 2006). However, the incremental benefit and safety of the maximum permissible dose of statin have not been confirmed (Dai , Huang , & Zhao , 2016). It also emphasized in 2016 Chinese guideline that most Chinese patients do not need and cannot tolerate high-intensity statin treatment and clearly gave a preference on moderate-intensity statin (Joint committee, 2016). Our results showed a consistency with those recommendations that most physicians preferred moderate-intensity statins for all four hypothetical patients. However, about one fourth preferred high-intensity statins on the diabetic patient though the LDL-C was not high. This also could be explained from another angle that Chinese physicians have a certain degree of recognition and agreement on high-intensity statins. Moreover, those who considered that high-intensity should not be routinely used in Chinese, were less likely to prescribe high-intensity statins on the hypertensive patient. This showed a consistency between physicians' attitudes and their prescriptions.

4.7. Non-statin drugs were advocated for persistent high LDL-C

Data from randomized study showed that a combination of moderate statin and ezetimibe achieved more reduction of LDL-C compared to the double-dose stain (Wu N. , et al., 2018)). In the 2016 Chinese guideline, ezetimibe was recommended as a collaborative drug for lowering blood cholesterol and fish oil, Fibrates were recommended for lowering non-HDL cholesterol. Our sample showed that only 57% would like to add ezetimibe in addition to statins when LDL-C and TC were uncontrolled, and almost no one reported a use of fish oil and fibrates. This may result from the high price of ezetimibe and fibrates in China. More studies on the reasons should be carried out.

4.8 Implications for policy and practice

The 2016 China guideline was established based on evidence from Chinese communities. The guideline made clear and specific recommendations for Chinese groups. Given its high adoption rate among Chinese physicians, we content that Chinese guideline could be further strengthening the implementation of the guidelines is imperative. However, physicians presented insufficient understanding of the guidelines. In particular, there was some ambiguity in the guidelines (e.g. initiation LDL-C of treatment), leading to a variety of inconsistencies in the way physicians approached statin treatment. Further evidence seeking to refine and supplement the evidence-based recommendations of the guidelines is critical. We strongly suggested the guideline

developers to collaborate with international guideline and evidence-based health care organizations (Chen, Wang, Shang, Yang, & Norris, 2018) to provide more evidence to solid their recommendations. An amendment of current Chinese guideline is indispensable to specify the confusions we presented.

To improve the high-quality adoption of the guideline, policy makers should establish a national system to collect, disseminate and implement guidelines, providing reliable assurance and control. Using online tools is a convenient and efficient way to achieve this goal. For example, referring to AHA/ACC online risks calculator (AHA/ACC, 2019), a similar online tool could be designed based on the 2016 Chinese guideline to facilitate adopters. Study conducted in the US showed that the physicians who used the risk calculators were more likely to prescribe statins on patients according to the guideline recommendations (Lowenstern, et al., 2018).

Moreover, since our findings also implied the impact of guidelines on physicians' attitude and the impact those attitudes on their reported statin prescriptions, training on physicians is necessary to properly direct physicians' attitudes and practice. A systematic review on guideline implementation indicated that print materials and educating professionals and patients were the most commonly employed strategies used for translating guideline to practice and 87.5% of them reported a positive impact (Gagliardi & Alhabib, 2015). In addition, online training platform is a novel and cost-effective instrument to facilitate guideline training as well. An online learning program in South

Africa significantly improve the adherence to brain injury guideline from 66.9% to 75.7% (Stassen, Wylie, & Holgate, 2015). This could be adopted in China as well.

4.8 Implications for further research

Our research needs a larger sample to involve physicians from different levels of hospitals and from remote areas in China. It is also necessary to conduct an observational study on their actual practice in clinical work, considering that all data was self-reported in our study. The similar study could be found in PLAM survey (Lowenstern, et al., 2018). Based on our results, we recommend further researches to focus on several controversial topics that found in our study. This includes reasons that physicians prefer different LDL-C target for treatment, whether and how they use risk stratification (what is the primary criteria), how do they practice on patients with hypertension, diabetes, stroke, and kidney diseases, what are reasons to use high-intensity statins. Some recommendations from 2016 Chinese guidelines were not convincing to our participants. It requires more evidence to testify the safety of high-intensity statin or find an optimal dose for the Chinese population. Additionally, a cohort study or case-control study is needed to confirm the association between physicians' attitudes and their reported statin prescriptions we found in this study.

4.9 Study strengths and limitations

4.9.1 Strengths

This was a well-designed online survey collecting comprehensive information. Using the most popular social application WeChat, we achieved a response rate over 70%. This is an innovative and cost-effective way to conduct survey that could be replicated in the further studies. To control the quality of the response, we only selected target hospitals and screened participant within those hospitals. Thus, we could make sure that all responses were from physicians at tertiary hospitals. We also used a password to enter the survey so that we can exclude other poor-quality responses. Missing data was generally small which made a limited impact on our results. Our study recruited participants across China which provided better representativeness and generalizability to the underling population. This study provided a good overview of physician attitudes and understandings on lipid management and guidelines and revealed some controversies which helped to direct further researches.

4.9.2 Limitations

When interpreting the results, some limitations should be considered cautiously. First, the representativeness may be a main concern in this study. During the data collection, our local collaborators used their own resource to screen and recruit participants. This could lead to collaborators recruiting doctors they knew and omitting unfamiliar ones. The participants we included were also disproportionately located, with only a small number of participants from the western part and most from the eastern part. Our sample showed more

female physicians and young physicians, and most were cardiologists. A comprehensive national survey showed that the average time of medical practice after receiving medical certification was 12.1 ± 8.5 years. Males and females accounted for 58.5% and 33.3% respectively. Similarly , national data on the general health workforce showed that male doctors were more than females (57% vs. 43%) (Anand, et al., 2008). Our sample was not complying with this proportion thus may be less representative to the underling population (Gong & Huo , 2016). Second, given the attribute of a cross-sectional study, the capability to interpret the causal relationship was weak in our study and the direction of the casual relationship we found may be adverse. Further cohort or case-control studies are needed to confirm our findings of the association. Third, recall bias was another critical issue in our study since all responses were self-reported. It could potentially bias our results and lead to misclassifications. Without the data from the real clinical practice, the significance of those practice patterns we measured was less reliable. Moreover, the sample size was not large enough to support a confidence level of 0.95 as we expected. From the literature review, the underline population size was estimated at approximately 10,000 (Gong & Huo, 2016). Thus, the sample size adjusted by population size was calculated as 369 at a confidence level of 0.95 (Qualtrics, 2018). However, our sample was smaller than expected size which reduces the confidence when interpreting the significant results. Last, this study took place in tertiary hospitals mainly in urban areas. This may overlook the importance of residence and hospital levels. Therefore, the results can only be generalized into physicians (cardiologists, endocrinologists, and general practitioners) in tertiary hospitals. Previous study has shown that statin prescription was different between urban and rural residences

(Chen, et al., 2011; Chen, et al., 2014). Thus, more participants from rural areas should be included and residence should be analyzed as a variable in further study.

5. Conclusion

Physicians in tertiary hospitals in China mainly adopted 2016 Chinese guideline to manage blood cholesterol which indicated its predominant role of guiding clinical practices and demanded of further strengthening of guideline implementation. However, the reported prescriptions of statins for different primary prevention patients by the guideline adopters were discordant with the recommendations. Thus, more training and education of this guideline was necessary. While most physicians in tertiary hospitals in China adopted 2016 guideline for the management of dyslipidemia in Chinese adults, the LDL-C target for treatment and practice of statins (prescription and dose) on hypothetical patients in primary and secondary prevention they reported showed insufficient consistency with the recommendations. Moderate-intensity statins were preferred by most, but high-intensity was also advocated by some physicians. Controversy could also be found in physicians' attitudes of statin safety on Chinese patients and some of their attitudes were associated with their prescriptions.

Large multi-center researches are called to provide more evidence-based recommendations. An amendment of current the 2016 Chinese guideline is necessary to clarify the current confusions. Appropriate training and intervention on the clinician population will contribute to the better drug prescription and compliance. The reasons behind the reported practice and the agreement between their reported practice and actual clinical practices is needed to evaluate.

Appendix A

Provider survey in China (2018)

S1 General Information

S1.1 Are you a

1. General practitioner
2. Cardiologist
3. Endocrinologist
4. Other _____

S1.2 Your gender is

1. Male
2. Female

S1.3 In which province do you work currently? _ _ _ _

S1.4 Your professional title is

1. Resident physician
2. Attending physician
3. Chief physician
4. Others, please describe:_____

S1.5 How long have you been in practice since you finished your training?

1. 0-5 years
2. 6-10 years
3. 11-20 years
4. 20+ years

S2 guideline adoption

S2.1 Which guideline do you primarily use to guide cholesterol management in your patients?

1. 2016 Chinese Guideline for the Management of Dyslipidemia in Adults
2. 2013 American College of Cardiology / American Heart Association(ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
3. American Association of Clinical Endocrinologists' (AACE) Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis
4. International Atherosclerosis Society (IAS) Global Recommendations for the Management of Dyslipidemia
5. European Society of Cardiology / European Atherosclerosis (ESC/EAS) Society Guidelines for the management of dyslipidemias
6. Other

7. None, I don't use any of these routinely to guide my practice

S2.3 In the following scenarios, please consider how you might approach lipid management for these asymptomatic and statin-naive patients:

S2.3.1 40 y.o. female non-smoker without comorbidities. BP 130/60. Total cholesterol 5.7mmol/L, LDL 4.3mmol/L, HDL 0.8mmol/L, BMI 29kg/m^2. How likely are you to recommend statin therapy? (click here to see 10-year risk: by ACC/AHA calculator: 2.4%, by: Framingham CVD calculator: 4.8%)

How likely are you to recommend statin therapy?

Very Unlikely	Unlikely	Neutral	Likely	Strongly Likely
❍1	❍2	❍3	❍4	❍5

What intensity statin would you recommend?

1. high intensity (Rosuvastatin 20-40 mg, atorvastatin 40-80 mg)
2. medium intensity (Rosuvastatin 10mg, Atorvastatin 10-20mg)
3. other

S2.3.2 45 y.o. male non-smoker without comorbidities. Current BP 150/110mmHg without treatment. Total cholesterol 5.0mmol/L, LDL 3.4mmol/L, HDL 0.8mmol/L, BMI 32kg/m^2. How likely are you to recommend statin therapy? (click here to see 10-year risk: by ACC/AHA calculator: 4.8%, by: Framingham CVD calculator: 12.2%)

How likely are you to recommend statin therapy?

Very Unlikely	Unlikely	Neutral	Likely	Strongly Likely
❍1	❍2	❍3	❍4	❍5

What intensity statin would you recommend?

1. high intensity (Rosuvastatin 20-40 mg, atorvastatin 40-80 mg)
2. medium intensity (Rosuvastatin 10mg, Atorvastatin 10-20mg)
3. other

S2.3.3 70 y.o. female non-smoker without comorbidities. Current BP 120/60. Total cholesterol 4.7mmol/L, LDL 2.8mmol/L, HDL 1.0mmol/L, BMI 22kg/m^2. How likely are you to recommend statin therapy? (10-year risk by ACC/AHA 8.7 %, Framingham CVD calculator 8.8%)

How likely are you to recommend statin therapy?

Very Unlikely	Unlikely	Neutral	Likely	Strongly Likely
❍1	❍2	❍3	❍4	❍5

What intensity statin would you recommend?

1. high intensity (Rosuvastatin 20-40 mg, atorvastatin 40-80 mg)
2. medium intensity (Rosuvastatin 10mg, Atorvastatin 10-20mg)
3. other

S2.3.4 51 y.o. male smoker with diabetes. Current BP 120/60. Total cholesterol 4mmol/L, LDL 2.3mmol/L, HDL 1.0mmol/L, BMI 20kg/m^2. How likely are you to recommend statin therapy? (10-year risk by ACC/AHA –12.6 %, Framingham CVD 22.1 %)

How likely are you to recommend statin therapy?

Very Unlikely	Unlikely	Neutral	Likely	Strongly Likely
❍1	❍2	❍3	❍4	❍5

What intensity statin would you recommend?

1. high intensity (Rosuvastatin 20-40 mg, atorvastatin 40-80 mg)
2. medium intensity (Rosuvastatin 10mg, Atorvastatin 10-20mg)
3. other

S2.4 Mr. C is a 64-year-old man with a prior stroke and claudication symptoms seeing you in clinic for routine follow-up. He has been on atorvastatin 80 mg daily without side effect for 1 year and very rarely misses a dose. His LDL is 3.4mmol/L, HDL 0.8mmol/L, and total cholesterol 5.7mmol/L. How would you treat this patient next?

1. No change in treatment
2. Change to a different statin
3. Add ezetimibe
4. Add fibrate
5. Add fish oil
6. Add bile acid sequestrant
7. Refer to lipid specialist
8. Other _____

S3 Statin intolerance

S3.1 Rate your agreement with the following statements

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
S3.1.1 I worry that the risks of statin therapy may be under-reported or under-appreciated	❍1	❍2	❍3	❍4	❍5
S3.1.2 High intensity statins should not be used routinely in Chinese patients	❍1	❍2	❍3	❍4	❍5
S3.1.3 Statins are extremely safe medications	❍1	❍2	❍3	❍4	❍5
S3.1.4 Statins are unnecessary in adults	❍1	❍2	❍3	❍4	❍5

with already low (<70 mg/dL) LDL levels					
S3.1.5 Statins are very effective in reducing risk of heart attack of stroke	❍1	❍2	❍3	❍4	❍5
S3.1.6 Statins prolong life	❍1	❍2	❍3	❍4	❍5
S3.1.7 Chinese patients are more likely to experience statin-related side effects than adults in other countries	❍1	❍2	❍3	❍4	❍5

S3.2 How often do you recommend any of the following for patients who report muscle aches while on statin therapy?

	Almost Never	Sometimes	Often
S3.2.1 Reduce the statin dose	❍1	❍2	❍3
S3.2.2 Reduce frequency of statin (e.g. take every other day)	❍1	❍2	❍3
S3.2.3 Stop the statin	❍1	❍2	❍3
S3.2.4 Switch to another statin	❍1	❍2	❍3
S3.2.5 Add Coenzyme Q to the statin	❍1	❍2	❍3
S3.2.6 Switch to non-statin lipid lowering medication	❍1	❍2	❍3
S3.2.7 Reduce physical activity or intense exercise	❍1	❍2	❍3
S3.2.8 Other_____			

S3.3 How often do you think statins may cause the following side effects?

	Never	Rarely	Occasionally	Often	Frequently
Myalgias (symptom with CK <40X ULN)	❍1	❍2	❍3	❍4	❍5
Muscle aches (symptom without CK elevation)	❍1	❍2	❍3	❍4	❍5
Hepatic injury	❍1	❍2	❍3	❍4	❍5
Memory Loss	❍1	❍2	❍3	❍4	❍5
Diabetes	❍1	❍2	❍3	❍4	❍5
Weakness	❍1	❍2	❍3	❍4	❍5

S4 Threshold of statin treatment

S4.1 At what level do you recommend initiation of statin therapy for adults with prior ASCVD?

1. LDL-C ≥30 mg/dL（0.8mmol/L）
2. LDL-C ≥50 mg/dL（1.3mmol/L）
3. LDL-C ≥70 mg/dL（1.8mmol/L）
4. LDL-C ≥100 mg/dL （2.6mmol/L）
5. LDL-C ≥130 mg/dL（3.4mmol/L）
6. No level
7. Other: _____

S5.2 What do you consider a treatment "goal" LDL-C level in adults with prior atherosclerotic cardiovascular disease?

1. LDL-C <30 mg/dL（0.8mmol/L）
2. LDL-C <50 mg/dL（1.3mmol/L）
3. LDL-C <70 mg/dL（1.8mmol/L）
4. LDL-C <100 mg/dL （2.6mmol/L）
5. LDL-C <130 mg/dL（3.4mmol/L）
6. No level
7. Other: _____

S5.3 What do you consider a "goal" LDL-C level in adults ***without*** prior atherosclerotic cardiovascular disease but who are at high-risk for ASCVD?

4 LDL-C <30 mg/dL（0.8mmol/L）
5 LDL-C <50 mg/dL（1.3mmol/L）
6 LDL-C <70 mg/dL（1.8mmol/L）
7 LDL-C <100 mg/dL （2.6mmol/L）
8 LDL-C <130 mg/dL（3.4mmol/L）
9 No level
10 Other: _____

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