IJC Metabolic & Endocrine 16 (2017) 16–20

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Statins use and the risk of liver dysfunction: A Chinese cohort study in real world clinical practice

Ying Gao [1], Yao Wang [1], Na-Qiong Wu, Cheng-Gang Zhu, Yuan-Lin Guo, Ping Qing, Geng Liu, Qian Dong, Jian-Jun Li *

Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

ARTICLE INFO

Article history:
Received 21 February 2017
Accepted 4 June 2017
Available online 13 July 2017

Keywords:
Statins
Liver
Aminotransferase
Cardiovascular disease

ABSTRACT

Background: The risk of liver injury is greatly of concern in China due to higher prevalence of hepatitis. In this study, we evaluated the association between the use of statins and the elevation of aminotransferase (ALT) in "real-world" clinical practice.

Methods: 4489 patients were divided into statins group (62%) and no statins group (38%) according to their status of medications. Detections of ALT were performed within 24 h after admission. The association of elevation of ALT and statins was analyzed.

Results: The percentage of patients with ALT > 1 × ULN(Upper Limit of Normal), was higher in statins group than that in no statins group (OR = 1.27, 95%CI 1.08–1.493), but after adjusting risk factors the OR value was 1.043(95%CI 0.851–1.278) with no statistical difference. Similarly, no differences were found regarding percentages of patients with ALT > 3 × ULN. Types of statins were usual in clinical practice and dosages of statins used were moderate in >90% of patient. We failed to find differences among the types and the dosage of statins except lovastatin. In addition, the relation of statin use duration to elevated ALT was evaluated. The higher proportion of elevated ALT in patients with stain use <1 month was detected compared those with stain use ≥3 months (OR = 1.408, 95%CI 1.111–1.783).

Conclusion: The data, firstly, provided two important information regarding the real status of liver dysfunction in Chinese patients who used moderate statins: 1) no relations between statin variety and ALT elevation; 2)statin-induced liver dysfunction frequently found in <1 month. Further study may be needed to confirm our findings.

1. Introduction

The HMG-CoA reductase inhibitors (statins) are widely prescribed for patients with hyperlipidemia and coronary heart disease. Statins reduce cardiovascular morbidity and mortality in high risk patients with or without hyperlipidemia [1]. As a result, statins are among the most frequently prescribed medications worldwide with over 143 million prescriptions annually dispensed in the United States alone [2].

Besides of the benefit impact of statins, the adverse effects such as liver dysfunction, myopathy and cognitive impairment have also been of greatly concern. Melissa Y, et al. found that the side effect of statins (complaining of muscle pain) was the primary reason for discontinuation (60%) [3]. Traditionally we test plasma aminotransferase (ALT) of the patients who use statins, so liver injury presented as plasma ALT elevations may also be the cause of discontinuation. Previous studies suggested that mild elevations in serum ALT arisen in up to 3% of treated patients, but clinically apparent drug-induced liver injury is rare [2]. In 2012, hence, the Food and Drug Administration (FDA) of the United States altered statin labeling such that unless clinically indicated for other reasons, after a pre-statin therapy baseline evaluation, follow-up liver enzyme testing was not uniformly required after statin initiation [4]. However, in HPS2-THRIVE study, excess of raised ALT was seen chiefly among the participants in China with excess of consecutive ALT > 3 × ULN(Upper Limit of Normal) of 0.24%/year compared with 0.02%/year in Europe [5]. As is known to all, the highest endemicity for HBV in the world is in the Western Pacific region. The north and central Asian countries including China have HBsAg prevalence rates as high as 10% to 12% [6]. This may be one of the reason that liver injury is more likely to occur in Chinese. Thus it can be seen that the data of the amount of patients who have statins-related liver dysfunction and the level of elevation of ALT were not available in Chinese population, especially a large cohort observation.

* Corresponding author.
E-mail address: lijianjun938@126.com (J.-J. Li).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The first two authors contribute equally to this study.

http://dx.doi.org/10.1016/j.ijcme.2017.06.003

2. Method

2.1. Study population

From March 2011 through February 2016, we consecutively recruited 8243 patients who were referred for diagnostic or interventional coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically indicated coronary computed tomography (CT) angiography. Patients with severe renal dysfunction (creatinine clearance rate <30 ml/min), active virus hepatitis, myocardial infarction related elevation of aminotransferase, heart failure (left ventricular ejection fraction <45%), significant instability of haemodynamics, infection or systemic inflammation, history or evidence of valvular heart disease, congestive heart failure, untreated thyroid disease, sinus node dysfunction or conduction disturbance, estrogen replacement therapy and carcinoma were excluded from the study. There were 4489 patients enrolled according to the exclusion criteria. The patients were divided into two groups. Group 1: patients who had taken statins before admission. Group 2: patients who had not taken statins before admission. Types of statins included simvastatin, atorvastatin, pravastatin, lovastatin, rosuvastatin, fluvastatin and pitavastatin. Patients who did not take statins were defined as those who did not take any lipid-lowering medicine including statins, fibrates, nicotinic acids, ezetimibe, probucol and omega-3 fatty acids for 3 months before admission (Fig. 1). The protocol was approved by Fu Wai hospital ethics committee. This study has been designed and conducted in accordance with the Declaration of Helsinki. All the patients have signed informed consents before enrolled in our study. Informed consent was obtained from all individual participants included in the study. For this type of study formal consent of ethics approval is not required.

2.2. Laboratory examinations

Blood samples were obtained for all patients from the cubital vein after a 12-h overnight fast within 24 h after admission. All the samples were tested in the clinical laboratory of Fuwai Hospital. The main index of liver function was alanine aminotransferase(ALT). CAD was defined as 1) any of the coronary artery such as the left main coronary artery (LM), the left anterior descending artery (LAD), the left circumflex coronary artery (LCX), right coronary artery (RCA) or the main branch of the vascular diameter stenosis reaching 50% or more; 2) who had prior coronary revascularization treatment; 3) any of the coronary artery had moderate to severe stenosis in computerized tomographic angiography (CTA). Hypertension was defined as blood pressure >140/90 mm Hg (at least 2 measurements under different conditions) or taking antihypertensive treatment. Diabetes was defined as fasting blood glucose >7.0 mmol/l or taking insulin or oral antidiabetic medicine.

2.3. Statistical analysis

Data were analyzed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD or median (Q1–Q3 quartile), and categorical variables were expressed as percentage. Comparison of categorical variables between the groups was performed using chi-square test. Comparison of

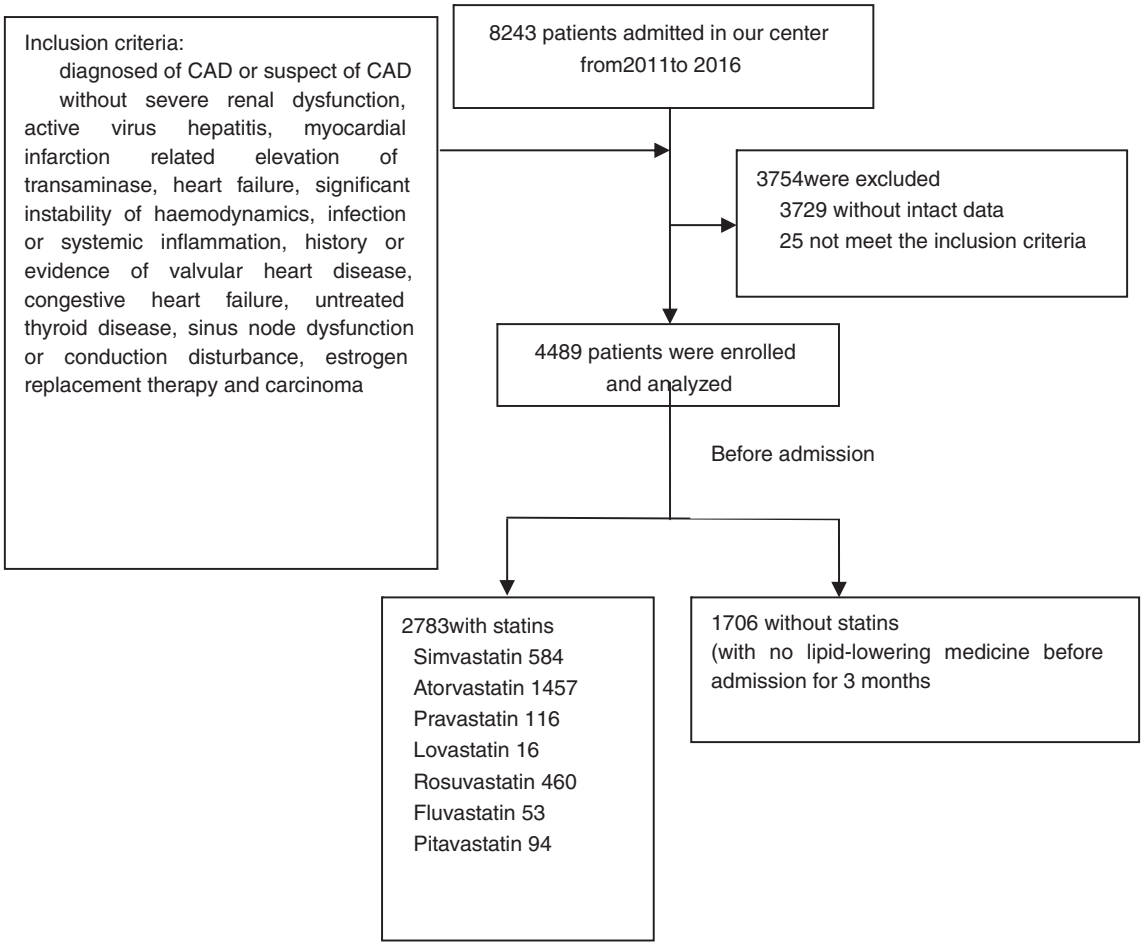

Fig. 1. Flowchart of patients enrolled in the study.

continuous variables between the groups was performed using independent sample *t*-test and Mann-Whitney *U* test. Logistic regression was used to evaluate the correlation between ALT levels in the statin group and the statin group. A p value <0.05 was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics

There were 4489 patients enrolled in our study, including 2783 patients with statins (62%) and 1706 patients with no statins (38%). The average age of the patients was 58.83 ± 10.24 years old. 3862 patients had CAD which statins group accounted for 90.9% and no statins group 78.1%. Baseline clinical characteristics of subjects were summarized in Tables 1 and 2. After comparing the baseline of two groups, we found that there were differences in age, sex, body mass index (BMI), co-morbidities, smoke, alcohol assumption, antiplatelet drugs, triglyceride and HDL-C which were adjusted in the next logistic regression analysis.

3.2. The relationship between statins and ALT elevation

Mild ALT elevation was defined as 1 × ULN < ALT ≤ 3 × ULN and moderate or severe elevation was ALT > 3 × ULN. There were 525 patients in statins group with mild ALT elevation, accounting for 18.9% of the statins group, while there were 264 cases in no statins group, accounting for 15.5% in no statins group. The differences between the two groups were significant (OR 1.27 95%CI 1.08–1.493 $p = 0.004$). However after adjusting risk factors such as age, sex, co-morbidities, smoke, drink and other prescriptions, we failed to find the difference (OR 1.043 95%CI 0.851–1.278, $p = 0.685$). In our study, there were 37 patients with ALT over 3 × ULN (1.33%) in statins group and 26 patients (1.53%) in no statins group. There were also no significant differences (OR 0.871 95%CI 0.525–1.443 $p = 0.603$) (Table 3).

3.3. The relationship between the types, dosage and duration of statin and the ALT elevation

There were 7 different statins containing all types of listing in China, including simvastatin, atorvastatin, pravastatin, lovastatin, rosuvastatin, fluvastatin and pitavastatin. More than half of the patients took atorvastatin. In the subgroup of lovastatin, we found lovastatin might induce ALT elevation whether mild or moderate and severe elevation (OR 4.269 95%CI 1.253–14.545 $p = 0.02$ and OR 7.845 95%CI 1.442–42.672 $p = 0.017$, respectively). Notably the case number of lovastatin group was rare. The relations with ALT elevation of other statins were not indicated.

According to the 2013 ACC/AHA guidelines for the treatment of cholesterol in adults, statins were divided into low intensity, medium intensity and high intensity dosage [7]. In our study 90.4% of the patients took the medium intensity of statins treatment. Only 2.7% of patients took high intensity of statins treatment. There were no significant differences between the dosage of statins and ALT elevation.

We also compared ALT in three groups according to the duration of statin use. The patients were divided into 3 groups according to the time of taking statins, which were <1 month, 1–3 months and ≥3 months. In <1 month group the proportion of the patients with mild ALT elevation was high compared with other subgroups (OR 1.408 95%CI 1.111–1.783 $p = 0.005$). While the duration of statin use were not related with ALT moderate or severe elevation (Table 3).

Table 2
Baseline characteristics of ALT elevation.

Characteristics	Normal ALT	ALT > 1 × ULN	*p* value
Age (SD)	58.94 ± 9.94	52.61 ± 10	<0.001
Male	2424 (65.5%)	677 (85.5%)	<0.001
BMI, kg/m^2(SD)	25.63 ± 3.32	26.18 ± 3.16	<0.001
Smoke	1844 (49.9%)	522 (66.2%)	<0.001
Drink	988 (26.7%)	295 (37.6%)	<0.001
DM	998 (27%)	162 (20.5%)	<0.001
Hypertension	2359 (63.8%)	451 (57.2%)	0.001
CAD	3158 (85.4%)	704 (89.2%)	0.004
TBIL (μmol/l)	13.7 (10.87–17.21)	13.6 (11.1–17.31)	0.761
Triglyceride (mmol/l)	1.44 (1.05–1.99)	1.66 (1.21–2.23)	<0.001
Total cholesterol (mmol/l)	4 (3.37–4.75)	3.98 (3.35–4.68)	0.35
HDL-C (mmol/l)	1.03 (0.87–1.24)	0.97 (0.83–1.14)	<0.001
LDL-C (mmol/l)	2.35 (1.83–3.04)	2.34 (1.83–2.97)	0.599
Antiplatelet drugs	2363 (83.8%)	542 (88.1%)	0.007
β blockers	1318 (47%)	314 (51.6%)	0.044
ACEI or ARB	671 (24.1%)	154 (25.4%)	0.497
Nitrates	1194 (42.6%)	266 (43.5%)	0.685
CCB	575 (20.7%)	109 (18%)	0.146
Diuretics	102 (3.7%)	14 (2.3%)	0.109

BMI body mass index, DM diabetes mellitus, CAD coronary artery disease, TBIL total bilirubin, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin-receptor blocker, CCB calcium channel blocker.

Table 1
Baseline characteristics between two groups.

Characteristics	ALT > 1 × ULN		*p* value	Normal ALT		*p* value
	Statins ($n = 2258$)	No statins ($n = 1442$)		Statins ($n = 525$)	No statins ($n = 264$)	
Age (SD)	52.66 (10.0)	52.5 (10.06)	0.827	58.92 (9.79)	58.98 (10.16)	0.856
Male	455 (86.7%)	222 (84.1%)	0.332	1532 (67.8%)	892 (61.9%)	<0.001
BMI, kg/m^2 (SD)	26.13 (2.94)	26.29 (3.55)	0.551	25.70 (3.18)	25.53 (3.54)	0.152
Smoke	352 (67.2%)	170 (64.4%)	0.473	1153 (51.1%)	691 (47.9%)	0.059
Drink	201 (38.6%)	94 (35.6%)	0.436	620 (27.5%)	368 (25.5%)	0.195
DM	115 (21.9%)	47 (17.8%)	0.192	623 (27.6%)	375 (26.0%)	0.305
Hypertension	301 (57.3%)	150 (56.8%)	0.939	1437 (63.6%)	922 (63.9%)	0.861
CAD	482 (91.8%)	222 (84.1%)	0.001	2047 (90.7%)	1111 (77.0%)	<0.001
Hypertriglyceridemia	222 (42.6%)	121 (46.0%)	0.402	708 (31.5%)	526 (36.7%)	0.001
Triglyceride (mmol/l)	1.64 (1.23–2.19)	1.7 (1.2-2.34)	0.351	1.41 (1.03–1.94)	1.48 (1.09–2.10)	<0.001
Hypercholesterolemia	27 (5.2%)	23 (8.8%)	0.063	96 (4.3%)	126 (8.8%)	<0.001
Total cholesterolemia	3.87 (3.28–4.56)	4.21 (3.4–4.97)	<0.001	3.78 (3.23–4.41)	4.41 (3.72–5.17)	<0.001
Low HDL-C	505 (97.1%)	258 (98.5%)	0.328	2141 (95.2%)	1343 (93.7%)	0.062
HDL-C (mmol/l)	0.98 (0.83–1.14)	0.97 (0.83–1.14)	0.914	1.01 (0.85–1.23)	1.06 (0.9–1.26)	<0.001
High LDL-C (>1.8 mmol/l)	392 (65.7%)	205 (34.3%)	0.374	1593 (70.8%)	1218 (85%)	<0.001
LDL-C (mmol/l)	2.27 (1.81–2.83)	2.56 (1.9–3.2)	<0.001	2.15 (1.73–2.7)	2.75 (2.13–3.4)	<0.001

BMI body mass index, DM diabetes mellitus, CAD coronary artery disease, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol.

Table 3
Relationship between duration, dosage and types of statins and ALT elevation.

	Mild ALT elevation			Moderate and severe ALT elevation		
	n	Adjusted OR (95% CI)	*p* value	n	Adjusted OR (95% CI)	*p* value
Statins group	525 (18.9%)	1.043 (0.851–1.278)	0.685	37 (1.3%)	0.830 (0.458–1.503)	0.539
Statin duration						
<1 month	265 (24%)	1.408 (1.111–1.783)	0.005	24 (2.2%)	1.331 (0.695–2.551)	0.389
1–3 months	58 (18.4%)	1.034 (0.712–1.503)	0.860	1 (0.3%)	0.222 (0.029–1.685)	0.145
≥3 months	202 (14.8%)	0.780 (0.610–0.996)	0.78	12 (0.9%)	0.547 (0.249–1.203)	0.134
Dose intensity						
Low	24 (12.9%)	0.654 (0.378–1.133)	0.13	1 (0.5%)	0.393 (0.052–2.991)	0.367
Middle	443 (19.2%)	1.083 (0.877–1.336)	0.459	29 (1.3%)	0.78 (0.416–1.463)	0.439
High	21 (30.4%)	1.621 (0.88–2.985)	0.121	1 (1.4%)	0.648 (0.079–5.301)	0.6862
Statin types						
Simvastatin	110 (18.7%)	1.011 (0.739–1.384)	0.943	8 (1.4%)	1.023 (0.420–2.493)	0.96
Atorvastatin	294 (20.2%)	1.14 (0.907–1.435)	0.261	18 (1.2%)	0.694 (0.339–1.421)	0.318
Pravastatin	13 (11.2%)	0.711 (0.362–1.395)	0.321	1 (0.9%)	0.722 (0.094–5.539)	0.754
Lovastatin	8 (50%)	4.269 (1.253–14.545)	0.02	2 (12.5%)	7.845 (1.442–42.672)	0.017
Rosuvastatin	80 (17.4%)	0.921 (0.673–1.259)	0.604	6 (1.3%)	0.764(0.296–1.972)	0.578
Fluvastatin	6 (11.3%)	0.536 (0.184–1.563)	0.254	1 (1.9%)	1.335 (0.169–10.573)	0.784
Pitavastatin	14 (14.9%)	0.867 (0.469–1.602)	0.649	1 (1.1%)	0.617 (0.080–4.765)	0.644

Low dose intensity (mg/d): Simvastatin 10, Pravastatin 10–20, Lovastatin 20, Fluvastatin 20–40, Pitavastatin 1; Middle dose intensity(mg/d): Atorvastatin 10–20, Rosuvastatin 5–10, Simvastatin 20–40, Pravastatin 40–80, Lovastatin 40, Fluvastatin 80, Pitavastatin 2–4; High dose intensity (mg/d): Atorvastatin 40–80, Rosuvastatin 20–40.

4. Discussion

Statins are one of the most important drugs for the prevention of cardiovascular events. Because statins inhibit a major liver enzyme in the synthesis of cholesterol, hepatic safety has been an ongoing concern and the potential liver toxicity of statins is still controversial. Only a small proportion of patients who participated in clinical trials with statins experienced transaminase elevations. Studies showed that only 0.1–2.7% of patients whose elevation of aminotransferase achieved 3 times of the ULN [8]. The risk of liver profile changes associated with statins seen in clinical trials is no greater in the placebo group when low or moderate dosages are used, <1%, and the rate reaches 3% with high dosages [9].The data of statin-related liver injury were mostly from well-designed clinical trials which had critical inclusion criteria and typically enrolled patients who were younger and healthier than those seen in routine practice. So we need the data in clinical practice to complete the concept.

In Taiwan, a population-based study including 4165 liver injury cases to examine the association between statins and hepatotoxicity showed that statin was not associated with risk of liver injury. However, data of Taiwan came from the claim data lack of laboratory value of liver function tests, so its conclusion had limitations [10].To the best of our knowledge, present study is the first large cohort, population based investigation to examine the relationship between statin use and liver dysfunction in Chinese population. Our study analyzed the use of statins in the real world. We found that the proportion of mild elevation of aminotransferase in patients who take statins was 18.9%, while the proportion of moderate or severe elevation of aminotransferase was 1.33%. It showed that the mild elevation of aminotransferase was significantly higher than that in the clinical trials, while the proportion of moderate or severe aminotransferase elevation was similar to that in clinical trials. But after adjusting the risk factors of ALT elevation, the association of the statins and ALT abnormalis was not significant. It suggested that statins could not induce ALT elevation which was consistent with clinical researches such as AFCAPS/TexCAPS study [11], 4S study [12], HPS study [13] and so on.

The elevation of aminotransferase related to statins mainly happened in 6 months after taking statins. Our study showed that the proportion of mild aminotransferase elevation was higher in short-term use of statins than that in long-term use of statins. The patients who took statins for <1 month had significant higher proportion of mild ALT elevation. Some studies suggested that the mild elevation of aminotransferase might be associated with inhibition of cholesterol synthesis or oxidative stress and inflammatory reaction of liver cells caused by statins [14]. Another reason might be the liver test had not be taken timely, so statins were not be ceased yet.

In western countries, there is a perfect system to monitor liver damage caused by drugs also known as DILI (Drug Induced Liver Injury), while in China DILI were reported mainly by outpatient Department or relevant institutions, so large-scale of epidemiological data were lacking. Therefore, there is no exact incidence of DILI in our country.

Apparently, our study provided a novel, important information with regard to linkage of the statin with liver dysfunction, especially, in Chinese population. Our study had some limitations. It was a cross-section study, which had no further observation and follow-up of patients with elevated aminotransferase. Additionally, relative small sample size may limit the significance of our study.

Our study shows the relationship of aminotransferase elevation with statins use in the real world. However, the mechanisms of mild elevation of aminotransferase related to statins are not clear. Finally our study shows that the elevation of aminotransferase is not associated with statins, which means statins are safe for treatment.

Declaration of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgement

This work was partially supported by the Capital Special Foundation of Clinical Application Research (Z121107001012015), the Capital Health Development Fund (2011400302, 201614035), and CAMS Major Collaborative Innovation Project (2016-I2M-1-011) awarded to Dr. Jian-Jun Li, MD, PhD.

References

[1] C. Baigent, A. Keech, P.M. Kearney, et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (9493) (2005) 1267–1278.
[2] M.W. Russo, J.H. Hoofnagle, J. Gu, et al., Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network, Hepatology 60 (2) (2014) 679–686.
[3] M.Y. Wei, M.K. Ito, J.D. Cohen, E.A. Brinton, T.A. Jacobson, Predictors of statinadherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education, J. Clin. Lipidol. 7 (5) (2013) 472–483.

[4] H. Bays, D.E. Cohen, N. Chalasani, S.A. Harrison, The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update, J. Clin. Lipidol. 8 (3 Suppl) (2014) S47–S57.
[5] HPS2-THRIVE Collaborative Group, HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment, Eur. Heart J. 34 (17) (2013) 1279–1291.
[6] H.S. Te, D.M. Jensen, Epidemiology of hepatitis B and C viruses: a global overview, Clin. Liver Dis. 14 (1) (2010) 1–21.
[7] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, J. Am. Coll. Cardiol. 63 (25 Pt B) (2014) 2889–2934.
[8] N. Chalasani, Statins and hepatotoxicity: focus on patients with fatty liver, Hepatology 41 (4) (2005) 690–695.
[9] E.V. Perdices, I. Medina-Cáliz, S. Hernando, et al., Hepatotoxicity associated with statin use: analysis of the cases included in the Spanish Hepatotoxicity Registry, Rev. Esp. Enferm. Dig. 106 (4) (2014) 246–254.
[10] G.L1. Chen, F.Y. Hsiao, Y.H. Dong, L.J. Shen, F.L. Wu, Statins and the risk of liver injury: a population-based case-control study, Pharmacoepidemiol. Drug Saf. 23 (7) (2014) 719–725.
[11] M. Clearfield, J.R. Downs, S. Weis, et al., Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women, J. Womens Health Gend. Based Med. 10 (10) (2001) 971–981.
[12] T.R. Pedersen, K. Berg, T.J. Cook, et al., Safety and tolerability ofcholesterol lowering with simvastatin during 5 years in theScandinavian simvastatin survival study, Arch. Intern. Med. 156 (1996) 2085–2092.
[13] Heart Protection Study Collaborative Group, MRC/BHF HeartProtection Study of cholesterol lowering with simvastatinin 20,536 high-risk individuals: a randomized placebo-controlledtrial, Lancet 360 (9326) (2002) 7–22.
[14] Group MBHPSC, J. Armitage, L. Bowman, R. Collins, S. Parish, J. Tobert, Effects of simvastatin 40 mg daily on muscle and liver adverse effects in a 5-year randomized placebo-controlled trial in 20,536 high-risk people, BMC Clin. Pharmacol. 31 (2009) (9:6).