Review Article

Use of Atorvastatin in Lipid Disorders and Cardiovascular Disease in Chinese Patients

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Abstract

Objective: Statins are still underused for the prevention of cardiovascular disease (CVD) in China. Hence, we conducted a systemic review on the pharmacology, clinical efficacy, and adverse events of atorvastatin, as well as on patient adherence.

Data Sources: We conducted a systemic search in PubMed with the following keywords: "atorvastatin" (Supplementary concept) or "atorvastatin" (All field) and ("China" [AD] or "China" [all field] or "Chinese" [All field]).

Study Selection: Clinical or basic research articles on atorvastatin were included.

Results: Atorvastatin is a reversible and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, decreasing the *de novo* cholesterol synthesis. The pharmacokinetics of atorvastatin among Chinese is similar to those in Caucasians, and several gene polymorphisms have proved to be associated with the metabolism of atorvastatin in the Chinese population. Several international multiple-center randomized control trials have demonstrated the benefit of atorvastatin for primary and secondary prevention of CVD. None of them, however, included the Chinese, and current evidence in the population is still inadequate, due to the small sample size, low study quality, short study duration, and the use of surrogate endpoints instead of clinical endpoints. The overall incidence of adverse events observed with atorvastatin did not increase in the 10–80 mg dose range, and was similar to that observed with placebo and in patients treated with other statins, which makes atorvastatin well-tolerated in the Chinese population. Moreover, high patient adherence was observed in clinical studies.

Conclusions: Based on the current available evidence, there is no significant difference between Chinese and non-Chinese population in term of pharmacology and clinical efficacy/safety. High-quality evidence is still needed to support the use of atorvastatin in high-risk Chinese population.

Key words: Atorvastatin; Cardiovascular Disease; Chinese; Dyslipidemia

Introduction

Numerous large-scale clinical trials have demonstrated that statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) substantially reduce cardiovascular (CV) morbidity and mortality in both primary and secondary prevention of CV disease (CVD).[1-3] A meta-analysis of individual data from 26 randomized trials of statins reported a 10% proportional reduction in all-cause mortality and a 20% proportional reduction in CV death/1.0 mmol/L (40 mg/dL) low-density lipoprotein-cholesterol (LDL-C) reduction. The risk of major coronary events was reduced by 23%, and the risk of stroke was reduced by 17%/mmol/L (40 mg/dL) LDL-C reduction.[3] Thus, most international guidelines on CVD prevention in clinical practice consider statin as the first-line medication of lipid-lowering treatment and recommend modulating the intensity of the preventive intervention according to the level of the total CV risk.[4-6]

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Atorvastatin, a member of the statins, was first synthesized in 1985. Since its approval by the US Food and Drug Administration in 1996, atorvastatin has become one of the best-selling drugs in pharmaceutical history. In China, atorvastatin is the most widely used lipid-lowering medication, accounting for about 40% of total statin use in secondary prevention of CVD.[7,8] Besides, the efficacy and safety of atorvastatin have been testified by more than 200 randomized controlled trials (RCTs), with most sufficient clinical evidence among all statins.[9] It is, therefore, important to evaluate the effect of atorvastatin in Chinese population. In this paper, we conducted a review on the appraisal and patient considerations in the use of atorvastatin in the Chinese population.

To identify all the relative literature involving the use of atorvastatin in the Chinese population, we conducted a systemic search in PubMed with the following keywords: "atorvastatin" (Supplementary concept) or "atorvastatin" (All field) and ("China" [AD] or "China" [all field] or

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"Chinese" [All field]). All clinical or basic research articles on atorvastatin in Chinese population were included in this review.

Pharmacology, Mechanism of Action, and Pharmacokinetics

Atorvastatin calcium is a calcium salt of a chiral, pentasubstituted pyrrole. Its molecular formula is C33H33CaFNO5, with a molecular weight of 582.6947.[10] Like other statins, atorvastatin is a reversible and competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol synthesis in the liver. Inhibition of the enzyme decreases *de novo* cholesterol synthesis.[11,12] Meanwhile, the partial depletion of cellular cholesterol by the action of the drugs leads to increasing expression of LDL receptors on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-C in the blood. Inhibition of cholesterol synthesis in hepatocytes results in a decrease in very LDL-C production and an indirect reduction in LDL-C.[13] Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of high-density lipoprotein-cholesterol (HDL-C), although the mechanism is still not entirely clear.[14]

Atorvastatin undergoes rapid absorption and preferential uptake by the liver when taken orally. The absolute bioavailability of the parent drug is about 14%, but the systemic availability for HMG-CoA reductase activity is approximately 30%.[14] The time to reach peak plasma levels (Tmax) varies from 0.5 to 6 h.[15] Administration of atorvastatin with food results in a prolonged Tmax, as well as in a reduction in maximum concentration (Cmax) and area under the curve (AUC), However, changes in the rate of atorvastatin absorption are not expected to have a clinically significant effect, as subsequent multiple-dose clinical studies have shown that dose, but not plasma atorvastatin concentration profiles, correlates with lipid-lowering effects.[16] Although the rate and the extent of equivalent absorption of atorvastatin were lower during evening than morning administration, the time of administration did not affect the plasma LDL-C-lowering efficacy of atorvastatin.[17] Atorvastatin is highly protein bound (≥98%). The major metabolic pathway of atorvastatin is through cytochrome P450 3A4 hydroxylation to form active orthohydroxylated and parahydroxylated metabolites, as well as various beta-oxidation metabolites. The orthohydroxylated and parahydroxylated metabolites are responsible for 70% of systemic HMG-CoA reductase activity. As a substrate for the CYP3A4, atorvastatin is expected to have drug-drug interaction with concurrent administration of potential inhibitors or inducers of this system.[18,19] Moreover, several genetic studies have found that CYP gene polymorphisms are associated with the metabolism of atorvastatin in the Chinese population and thus affect the lipid-lowering effect of atorvastatin [Table 1].[20-23] Atorvastatin is primarily eliminated via hepatic biliary excretion without entero-hepatic recirculation and <2% recovered in the urine. Atorvastatin has an approximate elimination half-life of 14 h. However, the HMG-CoA reductase inhibitory activity appears to have a half-life of 20–30 h, which is thought to be due to the active metabolites.[14]

Whether there is a differing pattern of systemic exposure to atorvastatin among Chinese versus Caucasian subjects was studied by Gandelman *et al*. by comparing data obtained from 310 Asians (31% Chinese) and 572 Caucasians in 22 pharmacokinetic studies. They found that the equivalent dose/bodyweight normalized AUC (Asian = 157.5, Caucasian = 156.4 [ng·h·ml^{-1}]/[mg/kg]) and Cmax (Asian = 26.2, Caucasian = 30.3 [ng/ml]/[mg/kg]) for atorvastatin were similar in both ethnic groups. They concluded that dosing considerations in atorvastatin are similar for Asian compared with Caucasian subjects.[24]

Efficacy of atorvastatin in lipid-lowering

A recent meta-analysis of 254 trials evaluating the dose-related efficacy of atorvastatin in 33,505 participants concluded that the blood total cholesterol, LDL-C, and triglyceride-lowering effect of atorvastatin were dependent on dose. Log dose-response data were linear over the commonly prescribed dose range. Atorvastatin of 10–80 mg/day resulted in 36%–53% decreases of LDL-C. However, there was no significant dose-related effect of atorvastatin on HDL-C.[9] To address the question of whether the lipid responses to atorvastatin may differ between Chinese and Caucasians, Hu *et al*. used the data from the direct statin comparison of LDL-C Values: An evaluation of rosuvastatin therapy (DISCOVERY) program. They found that there was a similar percentage reduction

Table 1: Gene polymorphisms associated with the metabolism of atorvastatin in chinese population

Authors, year	Study population	*n*	Target gene	Atorvastatin	Lipid lowering results
Gao *et al.*, 2008	Hyperlipidemic patients	217	CYP3A4*1G	20 mg/day × 4 weeks	TC*↓: 16.8% for the *1/*1 carriers, 17.8% for the *1/*1G carriers, and 20.9% for the *1G/*1G carriers
Li *et al.*, 2011	Hyperlipidemic patients	177	CYP3AP1*3	20 mg/day × 4 weeks	LDL-C†↓: 28.62% for the CYP3AP1*3/*3 carriers, and 25.53% for the CYP3AP1*1 carriers
Wei *et al.*, 2011	Hyperlipidemic patients	185	CYP7A1 A-204C ABCG8 C1199A	20 mg/day × 4 weeks	The CYP7A1-204A and ABCG8 1199A alleles appear to interact to affect triglyceride lowering response
Jiang *et al.*, 2012	Hyperlipidemic patients	170	CYP7A1	20 mg/day × 60 days	LDL-C↓: 27.89% for the GG/GA carriers and↓35.26% for the AA carriers

*Total cholesterol; †LDL-C: Low-density lipoprotein cholesterol.

in LDL-C in response to atorvastatin 10 mg/day in Hong Kong Han Chinese patients compared with those in patients from a mixture of other Asian or Western countries in the DISCOVERY program.[25]

Primary prevention of cardiovascular disease

The results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that hypertensive patients with mildly elevated cholesterol levels who took atorvastatin 10 mg daily had 36% fewer nonfatal myocardial infarction (MI) and fatal coronary artery disease than patients treated with placebo.[26] However, ASCOT only enrolled patients in the United Kingdom, Ireland, and Nordic countries. In a surrogate study from China, 151 patients with mild hypertensive were randomly divided into three groups: Atorvastatin 10 mg group, atorvastatin 20 mg group and the control group. After 3 months, LDL-C was decreased by 30% in the atorvastatin 10 mg group and 40.48% in the 20 mg group, consistent with the lipid-lowering effect in ASCOT. Carotid intima media thickness was decreased, and endothelial function was improved in both atorvastatin groups.[27] This result was further confirmed by Ge *et al*. A total of 126 hypertensive patients with hypercholesterolemia were randomized into amlodipine 10 mg/day group and amlodipine 10 mg/day plus atorvastatin 20 mg/day group. After 4 months of treatment with atorvastatin, serum total cholesterol, LDL-C, triglyceride, high sensitive-C reactive protein, and uric acid decreased significantly in the amlodipine plus atorvastatin group, while HDL-C increased ($P < 0.05$). Meanwhile, compared with that before treatment, left ventricular mass index in both groups decreased ($P < 0.05$), to a significantly lower degree in the amlodipine plus atorvastatin group than in the amlodipine group ($P < 0.05$).[28]

Type 2 diabetes mellitus (T2DM) is an important risk factor for developing CVD, and it has an atherogenic lipid profile consisting of elevated triglyceride and low HDL-C, which results in high non-HDL-C levels. In the Collaborative Atorvastatin Diabetes Study, 2,838 patients with diabetes aged 40–75 years in 132 centers in the United Kingdom and Ireland were randomized to placebo or atorvastatin 10 mg daily, and atorvastatin 10 mg daily is efficacious in reducing the risk of first CVD events by 37% (rate reduction 37%, 95% confidence interval [CI] - 52 to - 17; $P = 0.001$).[29] The ASCOT substudy further confirmed that atorvastatin 10 mg daily significantly reduced the risk of major CV events or procedures (hazard ratio [HR]: 0.77, 95%CI: 0.61–0.98; $P = 0.036$) among diabetic patients with well-controlled hypertension and without a history of coronary artery disease or markedly elevated cholesterol concentrations. The proportional reduction in risk was similar to that among participants who did not have diagnosed diabetes.[30] However, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in noninsulin-dependent diabetes mellitus, another RCT to access the efficacy of atorvastatin in subjects with T2DM failed to find a significant reduction in the primary composite end point comparing 10 mg of atorvastatin with placebo in both primary and secondary prevention (HR: 0.90, 95%CI: 0.73–1.12; $P = 0.34$), which may relate to the overall study design, the types of subjects recruited, sample size, and the protocol changes required because of changing treatment guidelines.[31] None of these three studies included Chinese population. Recently, Su *et al*. reported data of 151 diabetic patients treated with simvastatin 40 mg/day or atorvastatin 10 mg/day and found that both statins treatment significantly decreased plasma lipids in all patients with T2DM without a significant difference between the two groups. However, the effects of atorvastatin in increasing nitric oxide concentration and glutathione peroxidase, and superoxide dismutase activity, and in decreasing malondialdehyde level were significantly greater than those of simvastatin in patients with T2DM compared, suggesting that atorvastatin reduced oxidative stress more effectively than simvastatin did in patients with T2DM.[32] Liu *et al*. proved that both atorvastatin 10 mg/day and pravastatin 2 mg/day were effective in reducing the LDL-C level in Chinese diabetic patients, as well as in improving insulin resistance and endothelial function.[33] Another study also found that atorvastatin 80 mg/day has a similar effect on endothelial, platelet, and angiogenic indices in both South Asians and European with diabetes.[34]

A meta-analysis of 20 RCTs investigating different statins has demonstrated that using statins in a high-risk population for primary prevention is associated with a significant reduction in all-cause death, CV death, and major CV events.[2] This conclusion was confirmed by a recent network meta-analysis, and there is no significant difference between atorvastatin and other statins in primary prevention.[35] However, whether primary prevention is beneficial in individuals at low or modest risk is still uncertain.

Secondary prevention of cardiovascular disease

The Incremental Decrease in End Points through Aggressive Lipid Lowering trial found that intensive lowering of LDL-C with atorvastatin 80 mg/day did not result in a significant reduction in the primary outcome of major coronary events (HR: 0.89, 95%CI: 0.78–1.01; $P = 0.07$), but did reduce the risk of major CV events (HR: 0.87, 95%CI: 0.77–0.98; $P = 0.02$) and nonfatal acute MI (HR: 0.83, 95%CI: 0.71–0.98; $P = 0.02$) in patients with previous MI, when compared with usual dose simvastatin (20 mg/day).[36] Meanwhile in the treating to new targets study, 10,001 patients with stable coronary artery disease were randomized to receive atorvastatin 10 or 80 mg/day to achieve LDL-C goals of <100 and 70 mg/dL, respectively. Atorvastatin 80 mg/day reduced the risk of CV events to a significantly greater extent than atorvastatin 10 mg/day (HR: 0.78, 95%CI: 0.69–0.89; $P < 0.001$). However, the risk of overall mortality was similar in atorvastatin 80 mg/day recipients, compared with atorvastatin 10 mg/day recipients.[37] In China, 228 patients with stable atherosclerotic plaques who had undergone coronary arteriography and intravascular ultrasound were randomly assigned to receive placebo or atorvastatin at a single daily dose of 10 mg, 20 mg, 40 mg, or 80 mg. At 6 months

of follow-up, the LDL-C levels in the atorvastatin groups were below those at their respective baselines (All $P < 0.01$). The percentages of plaque necrosis following treatment in the placebo and atorvastatin 10 mg groups rose above baseline levels (15.51 ± 12.56 vs. 7.69 ± 1.31%, $P < 0.01$; 13.54 ± 11.76 vs. 7.83 ± 1.43%, $P < 0.01$, respectively) while the atorvastatin 20, 40, and 80 mg groups remained stable. Plaque volumes in the atorvastatin 40 and 80 mg groups decreased significantly compared with baseline plaque volumes (30.69 ± 8.12 vs. 37.09 ± 12.01 mm^3, $P = 0.019$; 24.99 ± 1.01 vs. 36.47 ± 14.68 mm^3, $P < 0.01$, respectively).[38]

Several large RCTs have been conducted to assess the efficacy of high-dose atorvastatin in patients with acute coronary syndrome (ACS). In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study, 3,086 patients with unstable angina pectoris or non-Q-wave MI were randomized within a mean of 63 h after hospitalization to receive atorvastatin 80 mg/day or placebo for 16 weeks in addition to usual therapy. Atorvastatin therapy reduced the incidence of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization compared with placebo (relative risk 0.84, 95%CI: 0.70–1.00; $P = 0.048$).[39] The Pravastatin or Atorvastatin Evaluation and Infection Therapy (IMPROVE IT-TIMI22) study enrolled 4162 patients who had been hospitalized for an ACS within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). After a 2 year follow-up, intensive lipid-lowering statin regimen provides greater protection against death or major adverse cardiac events (MACEs) (MI, documented unstable angina requiring rehospitalization, revascularization, and stroke) than a standard regimen (HR: 0.84, 95%CI: 0.74–0.95, $P = 0.005$).[40]

The efficacy of intensive lipid-lowering with high-dose atorvastatin in ACS patients has also been investigated in the Chinese population. In the study by Dong *et al*., 92 patients with ACS post successful percutaneous coronary intervention (PCI) were randomly divided into atorvastatin 10 mg/day and atorvastatin 40 mg/day on top of the standard medical therapy for 24 weeks. Total cholesterol and LDL-C in atorvastatin 40 mg/day group were significantly lower than in 10 mg/day group, as were the high sensitive-C reactive protein and Matrix metalloproteinases-9. Due to the small sample size, there is no difference in the incidence of MACEs between the two groups.[41] Another surrogate study by Zhao *et al*. further access the efficacy of high-dose atorvastatin in elderly Chinese patient with unstable angina and 166 patients with unstable angina who were ≥60 years of age, randomly assigned to receive atorvastatin 80 or 20 mg/day. Atorvastatin 80 mg/day was associated with a significant reduction in LDL-C, inflammatory factors, and improvement of endothelial function.[42] Yu *et al*. found that even a short-term pretreatment with a high dose of atorvastatin (80 mg 12 h before PCI, with a further 40 mg preprocedure dose) could reduce the 30 day incidence of MACEs in Chinese patient with non-ST elevation ACS (2.4% vs. 22.5%, $P = 0.016$), which mainly attributed to the reduction in the incidence of MI (2.4% vs. 20.0%, $P = 0.031$).[43] However, these studies have several limitations, including small sample size, low study quality, short study duration, and the use of surrogate endpoints instead of clinical endpoints.

Considering these limitations, several large RCTs have been initiated to evaluate the efficacy and safety of atorvastatin in Chinese patients with coronary artery disease. The China intensive lipid lowering with statins in ACS (CHILLAS) study is an open-label multicenter study in China to evaluate whether intensive treatment with statins for 2–5 years results in a greater reduction of CV events in patients with ACS compared with the standard statin therapy. A total of 1600 patients will be randomly assigned to receive intensive statin therapy (atorvastatin, 20 or 40 mg/day, or equivalent dose of other statins) or standard statin therapy (atorvastatin, 10 mg/day, or equivalent dose of other statins). The primary outcome of the study is the time to occurrence of cardiac death, nonfatal MI, revascularization with either PCI or coronary artery bypass surgery, documented unstable angina or severe heart failure requiring emergency hospitalization, and stroke. The CHILLAS study will be the first multicenter study in a Chinese population using a patient-level analysis to compare the effects and safety of intensive statin therapy with that of standard-dose statin therapy.[44] An Intensive statin therapy for Chinese patients with coronary artery disease undergoing PCI (ISCAP) study is also designed to evaluate the safety and efficacy of intensive statin therapy and the long-term outcome of patients in the Chinese population. Approximately, 1,100 patients with stable angina or non-ST elevation ACS undergoing selective PCI will be enrolled and randomized either to the intensive group (atorvastatin 80 mg/day × 2 days before and 40 mg/day × 30 days after PCI) or to the control group (usual care). The primary outcome is 30 day MACEs, and secondary outcomes are 6 months MACEs and change in biomarkers. The result of the ISCAP study will provide important evidence on the efficacy and safety of periprocedural serial intensive statin treatment in Chinese patients with coronary artery disease undergoing selective PCI.[45]

Safety, tolerability, and adherence of atorvastatin

Newman *et al*. conducted a pooled analysis from 44 clinical trials comprising 16,495 dyslipidemic patients to access the safety, tolerability, and adherence of atorvastatin in the 10 mg/day to 80 mg/day dose range. In this study, only 3% ($n = 241$) of atorvastatin-treated patients withdrew from studies due to treatment-associated adverse events, compared with 1% of those ($n = 16$) on placebo and 4% of those ($n = 188$) receiving other statins. The most frequently reported treatment-associated adverse events were related to the digestive system. Serious adverse events were rare and seldom led to the withdrawal. Elevations in alanine aminotransferase (ALT) were similar for both the

atorvastatin and the other statin treatment groups relative to the placebo group. Persistent ALT to >3 times the upper limit of normal (ULN) were experienced by 0.5% (n = 47) of atorvastatin-treated patients, compared with 1% of those (n = 16) on placebo and 4% of those (n = 188) receiving other statins. A persistent elevation in creatine phosphokinase (CK) (>10 ULN) was observed in only one atorvastatin-treated patient and was not associated with myopathy. The incidence of treatment-associated myalgia was low in the atorvastatin (1.9% [n = 181]), placebo (0.8% [n = 14]), and other statin (2.0% [n = 105]) groups, and was not related to the atorvastatin dose. No cases of rhabdomyolysis or myopathy were reported. The overall incidence of treatment-associated adverse events observed with atorvastatin did not increase in the 10–80 mg dose range and was similar to that observed with placebo and in patients treated with other statins. Specific analysis of musculoskeletal and hepatic adverse events showed that these infrequently occurred and rarely resulted in treatment discontinuation.[46] An updated pooled analysis of 49 clinical trials comparing the safety of atorvastatin 10 mg/day, atorvastatin 80 mg/day, and placebo further confirm that the incidence of treatment-associated adverse events for atorvastatin 80 mg/day was similar to that of atorvastatin 10 mg/day and placebo, as well as the incidence withdrawals due to treatment-related adverse events.[47]

To fully evaluate the safety and adherence of atorvastatin in the Chinese population, we conducted a systemic search of the literature in PubMed using the keywords "atorvastatin" (Supplementary concept) or "atorvastatin" (All field) and ("China" [AD] or "China" [all field] or "Chinese" [All field]) to identify all the RCTs comparing atorvastatin with control/placebo or other statins and reporting the incidence of side-effect. Thirteen RCTs with 4,145 patients were finally included [Table 2].[27,33,41-43,48-55] The incidence of hepatic and musculoskeletal toxicity and the adherence of medication were pooled using the Mantel-Haenszel Method with random effect model (STATA 11.0; STATA Corp., TX, USA). No case of rhabdomyolysis or CK > 10 ULN was reported. The risk of hepatic and musculoskeletal toxicity did not differ between atorvastatin and control/placebo groups, as well as the adherence of medication. Besides, atorvastatin has a similar risk of hepatic and musculoskeletal toxicity and adherence of medication with other statins. When compared with low-dose atorvastatin (10–20 mg/day), high-dose atorvastatin (40–80 mg/day) has a significantly higher risk of elevated ALT. However, the risk of elevated ALT > 3 ULN, as well as the risk of musculoskeletal toxicity and adherence to medications, did not differ between high-dose and low-dose atorvastatin. Thus, the overall incidence of significant adverse events observed with atorvastatin in Chinese population was similar to that observed with placebo or other statins [Figure 1].

Recently, statin therapy was found to be associated with an increased risk of development of diabetes,[56] and it is

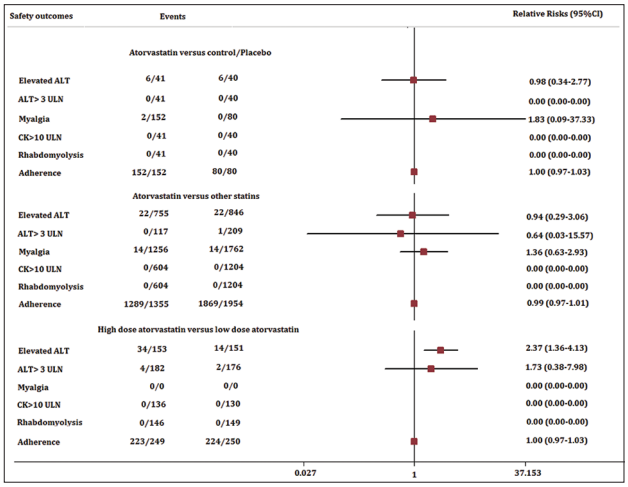

Figure 1: Pooled results of safety outcomes for atorvastatin in Chinese population.

believed that different types and doses of statins show different potential to increase the incidence of diabetes.[57] Compared with pravastatin, treatment with higher potency statins, especially atorvastatin and simvastatin, might be associated with an increased risk of new-onset diabetes.[58] However, a retrospective cohort study of 15,637 Chinese hypertensive and dyslipidemic patients demonstrated that patients who take atorvastatin or rosuvastatin are at lower risk of new-onset diabetes, while lovastatin and simvastatin were associated with a significant increase in the risk of new-onset diabetes.[59] Compared with lower-dose atorvastatin, atorvastatin 80 mg/day did not increase the incidence of new-onset diabetes in patients with 0 to 1 risk factors but did, by 24%, among patients with two to four risk factors for new-onset diabetes.[60] Of note, the risk of new-onset diabetes is low both in absolute terms and when compared with a reduction in coronary events.[56]

Limitations

First, only few studies were designed to compare the difference in use of atorvastatin directly between Chinese and western population. Thus, the major conclusions of the review were based on the indirect comparison. Second, high-quality evidence on atorvastatin, as well as the other statins, remained unavailable in Chinese population.

Conclusion

Although the benefit of atorvastatin in primary and secondary prevention has been verified by abundant of international multiple-center RCTs, none of them included the Chinese population, and the evidence of atorvastatin in the Chinese population is still insufficient. However, based on the current available evidence, there is no significant difference between the Chinese and non-Chinese populations in terms of pharmacology and clinical efficacy. Moreover, atorvastatin is well-tolerated and well-accepted by Chinese patients. Thus, atorvastatin still should be considered as one of the

Table 2: Safety outcomes and patients adherence of atorvastatin in randomized controlled trials with chinese population

Author, year	Study population	*n*	Duration	Primary outcomes	Intervention	Elevated ALT[||||]	ALT > 3 ULN[##]	Myalgia	CK*** > 10 ULN	Rhabdomyolysis	Adherence (%)
Dong *et al.* 2006	ACS*	92	24 weeks	hs-CRP[‖], MMP-9[#]	Atorvastatin 10 mg/day	9/46	2/46	NA[†††]	NA	NA	43/46 (93.5)
					Atorvastatin 40 mg/day	19/46	3/46	NA	NA	NA	42/46 (91.3)
Lam *et al.* 2006	Diabetes	29	12 weeks	Endothelin-1	Atorvastatin 40 mg/day	NA	NA	NA	NA	0/10	10/10 (100)
					Atorvastatin 20 mg/day	NA	NA	NA	NA	0/10	10/10 (100)
					Atorvastatin 10 mg/day	NA	NA	NA	NA	0/9	9/9 (100)
Gao *et al.* 2007	Hyperlipidemia	290	20 weeks	Lipid profile	Atorvastatin 10 mg/day	1/99	0/99	NA	0/99	0/99	93/99 (93.9)
					Rosuvastatin 10 mg/day	6/191	1/191	NA	0/191	0/191	183/191 (95.8)
Wu *et al.* 2007	Hypertension	151	12 months	CIMT**	Atorvastatin 10 mg/day	NA	NA	2/50	NA	NA	50/50 (100)
					Atorvastatin 20 mg/day	NA	NA	0/61	NA	NA	61/61 (100)
					Control	NA	NA	0/40	NA	NA	40/40 (100)
Yu *et al.* 2007	CAD[†]	112	26 weeks	CIMT	Atorvastatin 80 mg/day	2/57	NA	NA	NA	NA	54/57 (94.7)
					Atorvastatin 20 mg/day	1/55	NA	NA	NA	NA	53/55 (96.4)
Zhu *et al.* 2007	Hyperlipidemia high risk of CAD	1482	12 weeks	Lipid profile	Rosuvastatin 10 mg/day	NA	NA	8/995	0/995	0/995	942/995 (94.7)
					Atorvastatin 10 mg/day	NA	NA	4/487	0/487	0/487	465/487 (95.5)
Han *et al.* 2009	CAD post PCI[‡]	1275	12 months	MACE[††]	Atorvastatin 20 mg/day	21/638	NA	8/638	NA	NA	617/638 (96.7)
					Provastatin 20 mg/day	16/637	NA	5/637	NA	NA	621/638 (97.3)
Zhao *et al.* 2009	UA, >60 years	166	8 weeks	Inflammatory factors	Atorvastatin 80 mg/day	NA	1/86	NA	0/86	0/86	85/86 (98.8)
					Atorvastatin 20 mg/day	NA	0/80	NA	0/80	0/80	79/80 (98.8)
Sun *et al.* 2010	Non-ST elevation ACS	80	30 days	MACE	Atorvastatin 40 mg/day	0/20	0/20	0/20	0/20	0/20	20/20 (100)
					Atorvastatin (LD[‡‡]) 80 mg; (MD[§§]) 40 mg/day	0/20	0/20	0/20	0/20	0/20	20/20 (100)
					Atorvastatin (LD) 80 mg+40 mg; (MD) 40 mg/day	0/20	0/20	0/20	0/20	0/20	20/20 (100)
					Atorvastatin (LD) 80 mg+60 mg; (MD) 40 mg/day	1/20	0/20	0/20	0/20	0/20	20/20 (100)
Liu *et al.* 2011	Stable CAD	36	4 weeks	Endothelial function	Rosuvastatin 10 mg/day	0/18	0/18	0/18	0/18	0/18	18/18 (100)
					Atorvastatin 20 mg/day	0/18	0/18	0/18	0/18	0/18	18/18 (100)
Yu *et al.* 2011	Non ST elevation ACS	81	30 days	MACE	Atorvastatin(LD) 80 mg;(MD) 40 mg/day	6/41	0/41	0/41	0/41	0/41	41/41 (100)
					Placebo	6/40	0/40	0/40	0/40	0/40	40/40 (100)
Liu *et al.* 2013	High risk of CAD	251	12 weeks	Lipid profile	Pitavastatin 2 mg/day	NA	NA	1/112	NA	NA	105/112 (93.8)
					Atorvastatin 10 mg/day	NA	NA	2/113	NA	NA	96/113 (85)
Zhang *et al.* 2013	UA[§]	100	9 months	Progression of atherosclerotic plaques	Atorvastatin 80 mg/day	13/50	0/50	NA	0/50	0/50	32/50 (64)
					Atorvastatin 20 mg/day	4/50	0/50	NA	0/50	0/50	30/50 (60)

*Acute coronary syndrome; [†]Coronary artery disease; [‡]Percutaneous coronary intervention; [§]Unstable angina; [‖]High sensitive C reactive protein; [#]Matrix metalloproteinases; **Carotid intima thickness; [††]Major adverse cardiac event; [‡‡]Loading dose; [§§]Maintain dose; [||||]Alanine aminotransferase; [##]Upper limit of normal; ***Creatine phosphokinase; [†††]Not available.

first-line medication in Chinese patients with lipid disorders. However, high-quality evidence is needed to support the use of atorvastatin in high-risk Chinese population.

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