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# The Chinese-Han Population Carrying Wild-type Genotypes of SLCO1B1 388A>G, SLCO1B1 521T>C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3 Exhibits a Significant Alteration in the Pharmacokinetics of Atorvastatin Calcium

**Binbin Xia [a], Xianjun Liu [a], Yali Li [a], Yang Liu [a], Wenfang Sun [a], Jing Chen [a], Liushui Li [a], Jingyao Pang [a], Shicai Chen [a] and Hua Cheng [a*]**

*[a] Department of Pharmacy, Beijing Luhe Hospital Affiliated to Capital Medical University, Beijing, P.R. China.*

***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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**Corresponding author: E-mail: blw_blw@126.com;*

## ABSTRACT

Due to the diverse genetic characteristics of metabolism and high drug plasma exposure, great inter-subject variability exists in the clinical efficacy and incidence of adverse events. This study aimed to evaluate the associations between the SLCO1B1 388A＞G (rs2306283) polymorphism and the pharmacokinetics of atorvastatin calcium (AC) in healthy volunteers who carried the wild genotypes of SLCO1B1 521T＞C (rs4149056), CYP3A4 1B (rs2740574), CYP3A4 1G (rs2242480), and CYP3A5*3 (rs776746). A FISH technique was employed to investigate the genetic polymorphisms in 187 healthy male volunteers. The pharmacokinetic study was conducted on a group of healthy male Chinese-Han volunteers with wild-type genotypes of SLCO1B1 521T>C, CYP3A4 1B, CYP3A41G and CYP3A53 genes, consisting of either mutant heterozygotes (n=10) or mutant homozygotes (n=10) of SLCO1B1 388A>G. The results were then compared to the pharmacokinetic parameters of AC in subjects with the wild-type genotype of SLCO1B1 388A>G, as previously described. Based on the distribution of genotypes, the 187 volunteers could be divided into 28 groups. The top 10 groups accounted for nearly 85% of the total volunteers. No significant differences (P>0.05) were observed in the pharmacokinetic parameters between subjects carrying homozygous and heterozygous genotypes of SLCO1B1 388A>G. However, The $C_{max}$ of subjects carrying the wild-type genotype of SLCO1B1 388A＞G was about 14.75 times higher than that of the heterozygous genotype group and 10.43 times higher than that of the homozygous genotype group. The $AUC_{0\text{-}72h}$ of volunteers with the wild-type genotype of SLCO1B1 388A＞G was about 13.81 times higher than that of the heterozygous genotype group and 11.96 times higher than that of the homozygous genotype group. Volunteers carrying wild genotypes of SLCO1B1 388A＞G, SLCO1B1 521T＞C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3 showed significantly higher levels of $C_{max}$ and AUC (P<0.01), as well as markedly decreased values of CLz/F and Vz/F (P<0.01) of AC. In conclusion, patients carrying the wild genotype of SLCO1B1 388A>G, SLCO1B1 521T>C, CYP3A41G, CYP3A41B, and CYP3A5*3 should receive a lower dose of AC to minimize the risk of adverse effects.

*Keywords: Genetic polymorphism; SLCO1B1 388A＞G; SLCO1B1 521T＞C; CYP3A4 1*B; CYP3A4 1*G; CYP3A5*3; pharmacokinetics; atorvastatin calcium.*

## ABBREVIATIONS

*AUC : Area under the plasma concentration-time curve*
*BMI : Body mass index*
*$C_{max}$ : Maximum plasma concentration*
*TP : Total protein*
*ALB : Albumin*
*ALP : Alkaline phosphatase*
*ALT : Alanine aminotransferase*
*AST : Aspartate aminotransferase*
*TBIL : Total bilirubin*
*GGT : Glutamyltranspeptidase*
*CREA : Creatinine*
*BUN : Blood urea nitrogen*
*UA : Uric Acid*
*CK : Creatine kinase*
*- : Wild-type homozygote*
*+ : Mutant heterozygote*
*++ : Mutant homozygote*

## 1. INTRODUCTION

Atorvastatin calcium (AC) is widely used in clinical practice due to its ability to reduce the risk of heart and cerebrovascular events. Similar to other statins, AC works by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an essential enzyme in cholesterol biosynthesis. By lowering levels of low-density lipoprotein-bound cholesterol, AC can reduce the risk of atherosclerosis. The efficacy and safety of AC in facilitating the primary and secondary prevention of cardiovascular events have been demonstrated in various clinical trials [1-3]. However, due to the diverse genetic characteristics of metabolism and high drug plasma exposure, individual differences exist in clinical efficacy and adverse events, especially statin-induced myopathy [4,5].

Statin-induced myopathy is associated with elevated systemic drug exposure and can be increased by concomitant drugs that impair statin disposition and metabolism [6,7]. Other adverse drug reactions (ADRs) such as hepatotoxicity, reversible cognitive impairment, increases in glycosylated hemoglobin, and fasting serum glucose concentrations also impact the continuation of statin therapy [8]. AC is typically

administered orally at a specifies ranging from 10 to 80 mg/day. Once ingested, several enzymes and transporters participate in its metabolism and transport *in vivo*. Until recently, drug-metabolizing enzymes, such as cytochrome P450 enzymes (CYPs), were considered the major determinants of statin disposition [3,9-11]. Among these enzymes, those encoded by CYP3A4 and CYP3A5 are particularly important [12,13]. Data from *in vitro* studies have reported that CYP3A4 and CYP3A5 were responsible for 85% and 15% of atorvastatin metabolism, respectively [8,14]. AC is first transformed into its lactone form and subsequently into two pharmacologically active metabolites (2-hydroxy-atorvastatin and 4-hydroxy-atorvastatin) by these enzymes [3,15].

Aside from metabolic enzymes, AC also heavily rely on drug transporter proteins for its disposition and efficacy [3,6]. For instance, organic anion-transporting polypeptides and efflux transporter such as OATP 1B1, ABCB1, and ABCG2 are thought to play key roles in transporting statins into hepatocytes [6,8,14,16]. It has been reported that AC's intrinsic uptake clearance is 1900 μL/min/$10^6$ cells [17], and the relative contribution of OATP 1B1 to overall uptake clearance is more than 52.5 % [18,19] .

Two common genetic variations in SLCO1B1 (the encoding gene of OATP 1B1), 388A＞G (rs2306283) and 521T ＞ C(rs4149056), can interfere with the localization of the transporter to the plasma membrane, leading to higher systemic statin concentrations [3,6,8,16]. SLCO1B1 521T ＞ C (rs4149056) has been shown to interfere with the localization of the transporter to the plasma membrane, leading to decreased liver uptake and greater systemic statin concentrations, thereby resulting in increased muscle statin exposure responsible for statin-related myotoxicity [3,6,8,20]. On the other hand, the SLCO1B1 388A＞G(rs2306283) polymorphism has demonstrated a trend toward lower plasma statin levels in some healthy volunteer studies, although this association is not always observed [3,21]. SLCO1B1 genetic polymorphism has been reported as one of the determinants of inter-subject variability in simvastatin, pitavastatin, and rosuvastatin pharmacokinetics [22-24]. Significant variability in individual responses to AC administration has been observed, with studies suggesting that this variation in pharmacokinetics and lipid-lowering effects is influenced by related enzymes and transporters, in addition to the dosage form [3,25-27]. Therefore, it is necessary to study the effect of the specific gene polymorphism on the clinical pharmacokinetics of atorvastatin calcium while controlling for other related regulatory genes for enzymes and transporters.

The aim of this study was to evaluate whether the human gene polymorphism of SLCO1B1 388A ＞ G (rs2306283) affects the clinical pharmacokinetics of AC following the administration of single doses, taking into account the influence of SLCO1B1 521T＞C (rs4149056), CYP3A4 1B (rs2740574), CYP3A41G (rs2242480), and CYP3A5*3 (rs776746) genes. This evaluation was based on all subjects carrying the wild genotype of SLCO1B1 521T＞C, CYP3A4 1B, CYP3A41G, and CYP3A5*3 genes.

## 2. MATERIALS AND METHODS

### 2.1 Reagents and Chemicals

Atorvastatin calcium (Lipitor, Pfizer China) was obtained from Beijing Luhe Hospital Affiliated to Capital Medical University. Chemical reference substances of atorvastatin calcium (purity ≥98%) and rosuvastatin calcium (purity ≥98%) were purchased from the National Institute for Food and Drug Control (Beijing, China). PHARM-GENE 01 SNP analytical preservation solution (Yaojinbao®, Sino-Era Gene Tech Co. Ltd, Beijing, China) and PHARM-GENE 200 SNP analytical sample processing reagent (Yaojinfen®, Sino-Era Gene Tech Co. Ltd, Beijing, China) were respectively used as the reagent preservation solution and reagent analysis solution in the gene polymorphism analysis. Acetonitrile and methanol were purchased from Fisher Scientific (Fair Lawn, NJ, USA) as HPLC-grade solvents. Formic acid was purchased from Dikma Reagent Company (Beijing, China) as the HPLC-grade solvent. Triply distilled water was used in sample analysis. All other chemicals, reagents, and solvents used were of analytical grade.

### 2.2 Subjects and Study Design

A total of 210 Chinese-Han male volunteers aged 25-45 years were recruited for this research. The screening of healthy volunteers was accomplished by routine blood biochemical

examination, including hepatic-renal function. Gene mutations and polymorphism distribution of CYP3A53, SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A41G, and CYP3A41B in 187 healthy volunteers were identified using the FISH technique and SPSS software. This pharmacokinetic study was a single-center, randomized, open-label trial designed to evaluate the effects of genetic polymorphisms in SLCO1B1 388A>G on the pharmacokinetics of atorvastatin calcium (AC) in healthy subjects. The study was conducted on healthy male volunteers with SLCO1B1 388A>G genotypes of mutant homozygote (GG, n=10, Group A) and mutant heterozygote (AG, n=10, Group B). To minimize the influence of other related genetic factors, volunteers were required to have wild-type genotypes of SLCO1B1 521T>C, CYP3A4 1B, CYP3A41G, and CYP3A5*3 genes during the screening process. The obtained results were compared with the pharmacokinetics of AC in subjects with wild genotypes (AA, Group C) of SLCO1B1 388A ＞ G, SLCO1B1 521T ＞ C, CYP3A4 1B, CYP3A41G, and CYP3A5*3, as previously described by Xia et al. 2018.

This study was approved by the Ethics Committee of the Beijing Luhe Hospital affiliated to Capital Medical University. All participants provided written informed consent prior to any studyrelated procedure.

## 2.3 Instrumentation and Determination of AC Concentrations

The mass spectrometric data was recorded using an AB SCIEX QTRAP® 6500 mass spectrometer (AB SCIEX, USA), which was equipped with a 1290 Infinity II UHPLC system (Agilent Technologies, Palo Alto, CA, USA). The UHPLC system consisted of a G4220A 1290 binary pump, a G1379A vacuum degasser, a G4226 autosampler, and a G1330B 1290 column oven. Chromatographic separation was achieved using a Dikma Leapsil C18 column (100×2.1mm, 2.7μm). Data acquisition and quantitation were performed using Analyst 1.6.2® software (AB SCIEX, USA). The validated UHPLC-MS/MS method and a suitable protein precipitation method were applied to detect AC plasma concentrations, as previously described [4]. The calibration curves of AC were linear in the range of 0.05-50 ng/mL. The LLOQ was 0.05 ng/mL, and intra-day and inter-day precisions were below 11.69%. The accuracy was within the range of 100.40% to 108.03%.

## 2.4 Genotype Analysis

The genetic polymorphisms of SLCO1B1 388A>G, SLCO1B1 521T>C, CYP3A41B, CYP3A41G, and CYP3A5*3 were analysed using FISH technology with a gene amplification fluorescence detector (TL998A, Tianlong Science and Technology Co. Ltd, Xi'An, China). PHARM-GENE 01 SNP analytical preservation solution (Yaojinbao®, Sino-Era Gene Tech Co. Ltd, Beijing, China) and PHARM-GENE 200 SNP analytical sample processing reagent (Yaojinfen®, Sino-Era Gene Tech Co. Ltd, Beijing, China) were respectively used as the reagent preservation and analysis solutions in the genetic polymorphism analysis.

The polymorphism of the respective genes was analyzed according to the following procedure: (1) 2 mL venous blood was collected from each volunteer using a disposable vacuum blood collection tube (SST TUBE) containing EDTA anticoagulant. The SST tubes with anticoagulant fresh blood were vortexed for 15 seconds and preserved at 4 degree centigrade. (2) 150 μL anticoagulant fresh blood sample was added to a corresponding 1.5 mL centrifuge tube pre-added with 1 mL working liquid (ammonium chloride). After vortexing the centrifuge tube for 10 seconds, let it stand for 5 min. (3) Centrifugation was performed at room temperature at 3000 rpm/min for 5 min. The upper plasma was absorbed as clean as possible by a pipette (Eppendorf, Germany). 1 mL working fluid was added to the residual, which was enriched with white blood cells. The white blood cells were lightly repetitively beaten and washed by pipette, then centrifuged at room temperature at 3000 rpm/min for 5 min. The supernatant was discarded. (4) 50 μL PHARM-GENE 01 SNP analytical preservation solution (Yaojinbao®) was added to the centrifuge tube that contains enriched white blood cells. The sample solution was repetitively beaten and mixed by pipette, then let it stand at room temperature for 25 min, and shaken and mixed lightly 2 times during this period. (5) The corresponding PHARM-GENE 200 SNP analytical sample processing reagent (Yaojinfen®) was selected based on the type of gene to be detected (SLCO1B1 521T ＞ C, SLCO1B1 388A＞G, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3, respectively). 1.5 μL prepared white cells that treated with Yaojinbao® reagent were added precisely to the Yaojinfen® reagent. Then, the lid was tightly secured, and mixed uniformly. (6) The processed samples were tested and analyzed by TL998A type gene

amplification fluorescence detector. Data acquisition and quantitation were performed using the analysis software of the Individualized Pharmaceutical Service platform (Tianlong Science and Technology Co. Ltd, Xi'An, China).

### 2.5 Pharmacokinetic Study

To investigate the impact of the SLCO1B1 388A＞G gene on the clinical pharmacokinetics of AC, and to avoid the influence of other genes such as SLCO1B1 521T＞C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3, volunteers from groups 1, 2, and 6 in Table 3 were selected as Group A (GG, n=10), Group B (AG, n=10), and Group C (AA, n=5) [4] for the pharmacokinetic study. After an overnight fast, each participant received a single 40-mg oral dose of AC (2 tablets of Lipitor) with 100 mL of water. Licensed practical nurses used a venous indwelling needle (Needle-Free I.V. Catheter®, Linhwa Medical Equipment, Suzhou, China) and disposable vacuum blood collection tube (containing lithium heparin, BD, Franklin, NJ, USA) to collect blood samples. A 2 mL venous blood sample was collected at pre-dose, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 4.0, 8.0, 12.0, 24.0, 48.0, and 72.0 hours after oral administration of 40 mg Lipitor. The collected blood samples were then centrifuged at 3000 rpm for 10 minutes within 30 minutes. The supernatant plasma was collected, split into three equal parts, and stored at -80 degree centigrade until further use.

### 2.6 Statistical Analysis

DAS 2.1 software (professional edition, version 2.1.1, Drug and Statistics, Shanghai, China) was used to analyse the plasma pharmacokinetic data and calculate the parameters using a non-compartmental model. The pharmacokinetic parameters included maximum plasma concentration($C_{max}$), time taken for the drug to reach $C_{max}$ ($T_{max}$), the area under the concentration-time profile from 0 h to 72 h ($AUC_{0-72h}$), the area under the concentration-time profile from 0 h to infinity ($AUC_{0-\infty}$), the elimination of half-life time($t_{1/2}$), the clearance (CLz/F), the apparent volume of distribution(Vz/F), the mean residence time profile from 0 h to 72 h ($MRT_{0-72\ h}$), etc. The statistical analysis was performed SPSS Version 19.0 software (SPSS Inc., Chicago, USA). All data were presented as mean values ± standard deviation (Mean ± SD) unless otherwise indicated. The effects of genetic polymorphisms on the pharmacokinetic parameters of AC were assessed by the analysis of variance (ANOVA). Differences were considered statistically significant when $P < 0.05$.

## 3. RESULTS AND DISCUSSION

### 3.1 Demographics of the Total Individuals and Each Group of Volunteers

After a plasma biochemical examination, 187 healthy volunteers were identified out of 210 subjects who had passed the initial screening. These individuals exhibited normal liver function, with total protein (TP) levels within the range of 60-80 g/L, albumin (ALB) levels between 40-55 g/L, alkaline phosphatase (ALP) activity ranging from 15-112 U/L, alanine aminotransferase (ALT) levels of 0-40 U/L, aspartate aminotransferase (AST) levels of 0-40 U/L, total bilirubin (TBIL) concentrations within 1.71-17.1 μmol/L, gamma-glutamyl transferase (GGT) activity between 3-50 U/L, and normal kidney function, as indicated by creatinine (CREA) levels ranging from 44-115 μmol/L, blood urea nitrogen (BUN) levels within 2.1-7.9 mmol/L, and uric acid (UA) levels in the range of 149-417 μmol/L. These 187 healthy volunteers were then selected for further genetic polymorphism analysis of SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3. The demographics of the 187 individuals (referred to as the group of total volunteers) and each group of volunteers in this pharmacokinetic study (Groups A, B, and C) are summarized in Table 1.

### 3.2 Distribution of Genetic Polymorphisms

The frequencies and respective proportions of genotypes for SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3 were determined in a group of 187 healthy volunteers and are presented in Table 2.

The distribution of genotypes for SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4 1B, CYP3A4 1G, and CYP3A53 in the 187 volunteers was summarized and statistically analyzed. Based on the genotype distribution, the 187 volunteers were divided into 28 groups, and the top 10 groups accounted for nearly 85.0% of the total volunteers, as summarized in Table 3.

**Table 1. Baseline information and hepatic-renal function conditions of each group volunteer (Mean ± SD)**

| Category | | Total volunteers (n=187) | Group A (n=10) | Group B (n=10) | Group C (n=5) | Normal ranges |
|---|---|---|---|---|---|---|
| **Fundamental state** | Age (y) | 29.78±4.80 | 33.2±8.64 | 30.20±5.08 | 29.70±3.18 | - |
| | Height (m) | 175.41±4.27 | 172.40±2.24 | 174.20±4.24 | 174.40±4.40 | - |
| | Weight (kg) | 76.13±9.68 | 64.60±4.72 | 73.10±13.54 | 76.00±12.20 | - |
| | BMI | 24.70±2.75 | 21.70±1.24 | 23.84±3.38 | 24.86±3.18 | - |
| **Liver function test** | TP (g/L) | 72.89±2.88 | 71.42±1.74 | 72.77±3.04 | 74.69±4.63 | 60-80 |
| | ALB (g/L) | 48.98±1.51 | 47.60±0.72 | 48.10±1.20 | 48.94±2.13 | 40-55 |
| | ALP (U/L) | 78.86±13.81 | 66.4±11.12 | 74.00±15.00 | 86.70±15.04 | 15-112 |
| | ALT (U/L) | 27.79±14.46 | 28.4±14.24 | 23.40±9.44 | 27.80±11.80 | 0-40 |
| | AST (U/L) | 20.00±6.05 | 17.80±4.56 | 17.90±2.90 | 19.30±2.76 | 0-40 |
| | TBIL (μmol/L) | 13.85±4.06 | 14.02±4.14 | 12.86±4.83 | 11.05±4.81 | 1.71-17.1 |
| | GGT (U/L) | 37.45±20.91 | 39.20±25.44 | 38.80±25.12 | 31.70±8.84 | 3-50 |
| **Kidney function test** | CREA (μmol/L) | 76.54±6.91 | 74.40±7.52 | 75.10±5.70 | 76.10±5.90 | 44-115 |
| | BUN (mmol/L) | 4.75±0.83 | 4.54±1.00 | 4.80±0.63 | 5.494±1.15 | 2.1-7.9 |
| | UA (μmol/L) | 377.97±51.04 | 382.4±64.48 | 369.90±43.30 | 371.40±59.40 | 149-417 |

**Table 2. The frequencies of genotypes of SLCO1B1 521T＞C, SLCO1B1 388A＞G, CYP3A4 1*G, CYP3A4 1*G, CYP3A5*3 and respective proportion in 187 healthy volunteers**

| Genotyping | Genotype distribution | | | Sample size |
|---|---|---|---|---|
| | - | + | ++ | |
| **SLCO1B1 521T＞C** | 146 (78.07%) | 39 (20.86%) | 2 (1.07%) | 187 |
| **SLCO1B1 388A＞G** | 16 (8.56%) | 63 (33.69%) | 108 (57.75%) | 187 |
| **CYP3A4 1*G** | 117 (62.57%) | 64 (34.22%) | 6 (3.21%) | 187 |
| **CYP3A4 1*B** | 187 (100%) | 0 (0%) | 0 (0%) | 187 |
| **CYP3A5*3** | 109 (58.29%) | 65 (34.76%) | 13 (6.95%) | 187 |

*'-': wild-type homozygote; '+': mutant heterozygote; '++': mutant homozygote*

**Table 3. Classification of gene mutations of CYP3A5*3, SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4*1G and CYP3A4*1B in 187 healthy volunteers**

| Group | CYP3A5*3 (G>A) | SLCO1B1 521(T>C) | SLCO1B1 388(A>G) | CYP3A4*1G (C>T) | CYP3A4*1B (G>A) | Total Sample | Percentage (%) |
|---|---|---|---|---|---|---|---|
| **1(A)** | **-** | **-** | **++** | **-** | **-** | **37** | **19.79** |
| **2(B)** | **-** | **-** | **+** | **-** | **-** | **31** | **16.58** |
| **3** | + | - | ++ | + | - | 24 | 12.83 |
| **4** | - | + | ++ | - | - | 21 | 11.23 |
| **5** | + | - | + | + | - | 14 | 7.49 |
| **6(C)** | **-** | **-** | **-** | **-** | **-** | **9** | **4.81** |
| **7** | + | + | ++ | + | - | 7 | 3.74 |
| **8** | + | - | ++ | - | - | 6 | 3.21 |
| **9** | + | - | + | - | - | 4 | 2.14 |
| **10** | - | + | + | - | - | 4 | 2.14 |
| **11** | + | - | - | + | - | 3 | 1.60 |
| **12** | - | - | ++ | + | - | 3 | 1.60 |
| **13** | + | + | + | + | - | 2 | 1.07 |
| **14** | ++ | - | + | + | - | 2 | 1.07 |
| **15** | ++ | - | + | ++ | - | 2 | 1.07 |
| **16** | ++ | - | ++ | + | - | 2 | 1.07 |
| **17** | ++ | + | ++ | ++ | - | 2 | 1.07 |
| **18** | - | + | ++ | + | - | 2 | 1.07 |
| **19** | - | - | + | + | - | 2 | 1.07 |
| **20** | + | - | - | - | - | 2 | 1.07 |
| **21** | + | ++ | ++ | + | - | 1 | 0.53 |
| **22** | + | ++ | + | + | - | 1 | 0.53 |
| **23** | + | + | ++ | - | - | 1 | 0.53 |
| **24** | ++ | - | - | ++ | - | 1 | 0.53 |
| **25** | ++ | - | + | - | - | 1 | 0.53 |
| **26** | ++ | - | ++ | - | - | 1 | 0.53 |
| **27** | ++ | - | ++ | ++ | - | 1 | 0.53 |
| **28** | ++ | - | - | - | - | 1 | 0.53 |

*'-': wild-type homozygote; '+': mutant heterozygote; '++': mutant homozygote.*

**Table 4. The main pharmacokinetic parameters of AC in Group A (GG, n=10), Group B (GA, n=10) and Group C (AA, n=5) [4] subjects after oral administration of 40 mg Lipitor**

| Main parameters | Group A (Mean±SD) | Group B (Mean±SD) | Group C (Mean±SD) |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 13.00±6.91 | 9.15±4.85 | 135.59±50.03 |
| $T_{max}$ (h) | 2.59±1.59 | 2.87±1.39 | 2.4±0.894 |
| $AUC_{0\text{-}72h}$ (ng/mL*h) | 108.53±43.66 | 94.35±46.50 | 1298.15±266.12 |
| $AUC_{0\text{-}\infty}$ (ng/mL*h) | 111.47±42.58 | 95.83±46.27 | 1318.48±290.61 |
| $t_{1/2}$ (h) | 10.22±1.94 | 8.43±2.37 | 8.30±2.36 |
| CLz/F (L/h) | 406.63±151.84 | 504.83±227.39 | 31.49±6.61 |
| Vz/F (L) | 6174.95±2871.59 | 6624.72±4353.59 | 392.95±183.39 |
| $MRT_{0\text{-}72h}$ (h) | 11.43±1.91 | 11.33±2.42 | 11.25±3.11 |
| $MRT_{0\text{-}\infty}$ (h) | 12.74±1.69 | 12.23±2.68 | 11.74±3.01 |

Among these groups, the largest population among the 187 subjects was volunteers carrying the wild type of SLCO1B1 521T>C, CYP3A4 1B, CYP3A4 1G, CYP3A53, and mutant homozygote of SLCO1B1 388A>G (GG, Group 1 in Table 3, named as Group A), comprising 19.79% of the total. The second-largest group (16.58% of the total) comprised subjects carrying the wild type of SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4 1B, CYP3A4 1G, and mutant heterozygote of SLCO1B1 388A>G (GA, Group 2 in Table 3, named as Group B). The volunteers who carried all the wild genotypes of SLCO1B1 521T>C, SLCO1B1 388A>G, CYP3A4 1B, CYP3A4 1G, CYP3A5*3, and SLCO1B1 388A>G (AA, Group 6 in Table 3, named as Group C) comprised only 4.81% of the 187 subjects.

### 3.3 Effect of SLCO1B1 388A ＞ G Polymorphisms on AC Pharmacokinetics

To investigate the impact of the SLCO1B1 388A ＞G gene on the clinical pharmacokinetics of AC, and to avoid the influence of other genes such as SLCO1B1 521T＞C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3, volunteers from groups 1, 2, and 6 in Table 3 were selected as Group A (GG, n=10), Group B (AG, n=10), and Group C (AA, Xia et al. 2018) for the pharmacokinetic study. A validated UHPLC-MS/MS method was successfully applied to the pharmacokinetic study of Group A and Group B after the oral administration of Lipitor at a dose of 40mg. The relevant pharmacokinetic parameters of AC in each group were calculated by DAS 2.1 software. The acquired results were then compared with the pharmacokinetics of AC in Group C, which was described previously [4]. The relevant pharmacokinetic parameters of AC in Group A, B, and C are summarized and presented in Table 4.

## 3.4 Discussion

No significant differences ($P > 0.05$) were observed in the pharmacokinetic parameters between Group A and Group B. However, Group C showed significantly higher $C_{max}$ and AUC values ($P < 0.01$), as well as markedly lower values of CLz/F and Vz/F ($P < 0.01$) compared with Group A and Group B. $C_{max}$ was found to be the best parameter for revealing differences in pharmacokinetic profiles, and $AUC_{0-t}$ was considered to be the best parameter for evaluating inter-individual pharmacokinetic variation of a drug [28]. Previous studies have reported that genetic variation can cause >10-fold variations in the pharmacokinetic parameters of AC, namely $C_{max}$ and AUC [28], and marked interpatient variability in plasma levels, particularly at higher doses [29].

Several studies have investigated the impact of SLCO1B1 genetic variations on the efficacy of different statins, particularly atorvastatin and simvastatin. However, these studies have yielded controversial results [30-38]. For instance, the rs4149056 (SLCO1B1 521T > C) and rs2306283 (SLCO1B1 388 A > G) polymorphisms have been found to affect the amino acid sequence of the SLCO1B1 gene product. The presence of the rs4149056 SNP has been associated with a reduced LDL cholesterol-lowering response to pravastatin in elderly patients [32], while no significant effect has been observed with the rs2306283 SNP [32]. In the Emirati population, the prevalence of the rs4149056 C allele, which is linked to statin-induced myopathy, was lower compared to Caucasians and Africans. However, patients with this allele showed a trend of higher glycosylated hemoglobin and BMI despite having a normal lipid profile [33].

Regarding atorvastatin, an extensive analysis has revealed that the SLCO1B1 521T > C and SLCO1B1 571T > C SNPs may affect the inter-individual response to the drug. However, further studies with larger sample sizes are needed to confirm this finding [37]. The impact of the SLCO1B1 388 A > G SNP on OATP1B1 transport activity and the lipid-lowering efficacy of pitavastatin has shown conflicting results. One study reported elevated levels of $C_{max}$ and $AUC_{0-\infty}$ of pitavastatin in individuals carrying the 388GA and 388GG genotypes, while another study found no significant influence in Chinese volunteers [22]. Furthermore, OATP1B1 388A>G polymorphism plays a significant role in the pharmacokinetics of pitavastatin in healthy Chinese volunteers, and this may provide one interpretation for the inter-difference in pitavastatin disposition [34].

Additionally, studies conducted in Thai, Greek, and Chinese populations failed to establish a significant association between SLCO1B1 polymorphisms (c.388A>G, c.521T>C, g.89595T>C, 411G>A, c.597C>T and *439T>G ) and the lipid-lowering response to simvastatin or atorvastatin [39,21,35,36]. Similar frequencies of the SLCO1B1 521T>C and 388A>G variants were observed in Chinese patients with essential hyperlipidemia compared to healthy Chinese and

Japanese individuals, but these frequencies differed significantly from Caucasians and blacks [35]. In a study involving Macedonian subjects, no significant association was found between different SLCO1B1 genotypes and atorvastatin response [36].

These conflicting conclusions may arise due to variations in the genetic mutations involved in different populations.For instance, the genotype frequencies of SLCO1B1 388A>G differed significantly between Chinese-Han and the Greek population. In the Chinese-Han population, the genotype frequencies of wild-type homozygote, mutant heterozygote, and mutant homozygote of SLCO1B1 388A>G were 8.56% (AA), 33.69% (AG) and 57.75% (GG), respectively [4]. However, in the Greek population, the genotype frequencies were 32.0% (AA), 49.4% (AG), and 18.6% (GG), respectively [21]. The genotype frequencies of SLCO1B1 388A>G was significant difference in different crowds [4,21,40]. This suggests that population-specific differences in genotype frequencies may contribute to the contradictory findings. Furthermore, the interactions of other atorvastatin-lipid-related gene polymorphisms (e.g. CYP3A polymorphisms) were not taken into consideration in all those studies.

In the present study, the $C_{max}$ of subjects carrying the wild-type genotype of SLCO1B1 388A＞G was about 14.75 times higher than that of the heterozygous genotype and 10.43 times higher than that of the homozygous genotype, as shown in Table 4. The $AUC_{0\text{-}72h}$ of volunteers with the wild-type genotype of SLCO1B1 388A＞G was about 13.81 times higher than that of the heterozygous genotype and 11.96 times higher than that of the homozygous genotype, as shown in Table 4. These results confirm that carriers of the wild-type genotype of SLCO1B1 388A＞G exhibit higher absorption of AC and decreased uptake of AC into the liver, resulting in increased plasma concentration. The CLz/F values of subjects carrying the wild-type genotype of SLCO1B1 388A＞G were about 6.24% for the heterozygous genotype and 7.74% for the homozygous genotype, as shown in Table 4. The Vz/F value of Group C was about 5.93% for Group B and 6.36% for Group A, as shown in Table 4. However, no significant differences were observed in the value of $T_{max}$, $t_{1/2}$, or $MRT_{0\text{-}72h}$ for AC among these groups ($P＞0.05$), as shown in Table 4.

Currently, AC is definitely the most commonly prescribed lipid-lowering drug in China. Despite the relatively low risk of undesirable side effects of AC, an increasing number of patients are presenting with adverse reactions, which can be attributed to the very high prescription rate of AC [38]. The current study indicates that carriers of the wild type genotype of SLCO1B1 388A＞G have higher levels of $C_{max}$ and AUC of AC, while a markedly diminished clearance activity of AC is observed in carriers of the wild type genotype. According to the Lipitor label, patients who took 40mg of Lipitor for a long time had a 5.1% higher incidence of myalgia than those who took placebo. The proportion of subjects carrying wild genotypes of SLCO1B1 388A＞G, SLCO1B1 521T ＞ C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3 genes was about 4.81% in this study (shown in Table 3), which is roughly equivalent to the incidence of myalgia after taking Lipitor (5.1%). This might be one of the causes of adverse reactions in a very few patients after taking AC.

In the current study, the effect of the SLCO1B1 388A ＞ G genetic polymorphism on AC pharmacokinetics was evaluated for the first time, based on all subjects carrying wild genotypes of SLCO1B1 521T＞C, CYP3A4 1B, CYP3A4 1G, and CYP3A5*3 genes. Interestingly, unexplained high creatine kinase (CK) levels ( ＞ 1000 U/L) with no clinical symptoms were observed in several volunteers according to the plasma biochemical examination data in the initial 210 subjects. This might be another cause of adverse reactions in a very few patients after taking AC.

The limitations of this study are two fold. Firstly, the exclusive recruitment of male volunteers restricts the generalizability of the findings to the broader population, including females. Including female participants would have provided a more comprehensive understanding of potential gender-specific effects on drug pharmacokinetics. Therefore, caution should be exercised when extrapolating the study's results to females. Future studies should aim to include a diverse sample that represents both males and females to ensure a more representative analysis. Secondly, the study overlooked the influence of ABC transporters, specifically ABCB1 and ABCG2, which are known to have a significant impact on drug transport and metabolism [8,23,41-43]. These transporters play an important role in drug disposition, and

considering common polymorphisms in these transporters would have provided valuable insights into their contribution to the observed drug pharmacokinetics. Incorporating ABC transporters as potential factors in future research would enhance our understanding of their influence on drug response. Therefore, it is important to acknowledge that the findings of this study may not fully capture the effects of SLCO1B1 polymorphisms on statin efficacy in the general population. Further research is warranted to gain a comprehensive understanding of the association between SLCO1B1 polymorphisms and the effectiveness of statins in diverse populations. It is crucial to consider population-specific variations in genotype frequencies, as well as genetic polymorphisms involved in the metabolism and transport of statins, when investigating the impact of genetic variations on drug response. By addressing these limitations, future studies can improve the clinical applicability and relevance of their findings.

## 5. CONCLUSION

This study highlights the importance of genetic testing in predicting both the response and potential adverse reactions to lipid-lowering drugs. It examined how genetic variations affect the pharmacokinetics of AC, revealing that individuals with wild type genotypes exhibit higher levels of $C_{max}$ and AUC, along with reduced clearance activity. These findings suggest that genetic variations in drug metabolism and transporters can significantly affect drug efficacy and safety.

The most significant finding of this study is the effect of SLCO1B1 388A>G genetic polymorphism on the pharmacokinetics of AC, taking into account the influence of SLCO1B1 521T＞C (rs4149056), CYP3A4 1B (rs2740574), CYP3A41G (rs2242480), and CYP3A5*3 (rs776746) genes. The SLCO1B1 gene encodes the hepatic uptake transporter OATP1B1, which plays a critical role in the transport of AC into hepatocytes. The functionally important SNPs of this gene can lead to significant inter-individual variability in plasma concentration of AC, thereby affecting the therapeutic efficacy and the risk of associated adverse effects. Several studies have reported an association between SLCO1B1 polymorphisms and the risk of myopathy in patients receiving AC [20]. This study also found that unexplained high CK levels (＞1000 U/L) were observed in some volunteers, which could be another cause of adverse reactions in a few patients after taking AC. Elevated CK levels are a recognized marker of muscle damage and are commonly used to monitor the risk of myopathy in patients receiving lipid-lowering drugs [44].

Overall, the results of this study support the current clinical practice of individualized dosing of lipid-lowering drugs based on genetic testing. Patients who carry wild-type genotypes of SLCO1B1 388A>G, SLCO1B1 521T>C, CYP3A41G, CYP3A41B and CYP3A5*3 should receive lower doses of AC to minimize the risk of adverse reactions. This approach may improve the safety and efficacy of AC treatment and reduce the economic burden associated with managing adverse events. In conclusion, genetic testing can provide valuable information for personalized dosing and management of lipid-lowering drugs. Further research is needed to validate the findings of this study in larger patient populations and to identify additional genetic markers that can predict the response and adverse reactions to AC and other lipid-lowering drugs.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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