Original Article

A Study Protocol on the Overlooked Role of ABCB1 Pharmacogenetics in Atorvastatin Therapy: A Systematic Review of Clinical, Pharmacokinetics, and Population Evidence

***Yusuf OA[1], Tamuno I[2]**

[1]*Department of Clinical Pharmacology & Therapeutics, Faculty of Basic Clinical Sciences, Federal University of Health Sciences, Azare, Bauchi State, Nigeria.*

[2]*Department of Clinical Pharmacology, Faculty of Basic Clinical Sciences, Bayero University, Kano State, Nigeria.*

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***Correspondence:** Yusuf O.A
Email: olalekan.yusuf@fuhsa.edu.ng

ABSTRACT

Atorvastatin is widely used for dyslipidaemia and cardiovascular disease prevention, yet interindividual variability in efficacy and adverse effects, particularly statin-induced myopathy, limits its clinical use. Pharmacogenetic studies have largely focused on SLCO1B1 and CYP3A4/5; the role of ABCB1, which encodes P-glycoprotein, remains underexplored. This review aims to systematically evaluate the influence of ABCB1 polymorphisms on atorvastatin pharmacokinetics, efficacy, and safety outcomes. Following PRISMA guidelines, clinical studies involving adults on atorvastatin therapy will be identified from PubMed, Web of Science, and Scopus. Eligible studies must assess associations between common ABCB1 variants (e.g., C3435T, G2677T/A, and C1236T) and atorvastatin response outcomes. Data on study design, population, demographics, genotyping, and other key findings will be extracted. The risk of bias will be assessed using the Newcastle-Ottawa Scale for observational studies, and a meta-analysis will be performed. The review will clarify the contribution of ABCB1 polymorphisms to atorvastatin pharmacokinetics, lipid-lowering efficacy, and adverse events. It will also explore ethnic differences in allele frequencies and treatment response. By addressing this overlooked aspect of statin pharmacogenetics, the insights gained may support the integration of ABCB1 genotyping into clinical decision-making and enhance personalised cardiovascular therapy.

Keywords: ABCB1; Genetic polymorphism; Atorvastatin; Pharmacokinetics; Personalized medicine; Adverse drug reactions

INTRODUCTION

Atorvastatin is one of the most widely prescribed statins for managing hyperlipidaemia and preventing cardiovascular disease[1]. This drug is an HMG-CoA reductase inhibitor (statin) that lowers low-density lipoprotein cholesterol (LDL-C) and Triglycerides and is very effective in reducing atherosclerosis and cardiovascular disease[2]. Previous studies had revealed that elevated LDL-C is a key independent risk factor for the pathogenesis and recurrence of cerebral ischaemic stroke[3]. To reduce LDL-C level, atorvastatin has been employed, thereby decreasing the incidence, recurrence, disability, and mortality associated with cerebral ischaemic stroke[4]. In addition, atorvastatin also reduces damage to the kidney through its anti-inflammatory, antioxidative, and anti-cell proliferative effects[5]. While its clinical efficacy is well established, interindividual variability in response and adverse drug reactions (ADRs), particularly statin-induced myopathy and peripheral neuropathy, remain significant challenges[6].

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Atorvastatin calcium salt is administered orally, absorbed into the blood through the small intestine, and transported by the OATP transporter into hepatocytes, where it is metabolised by CYP3A4 and CYP3A5 to a bioactive metabolite[7]. The OATP1B1 transporter, encoded by SLCO1B1, is largely responsible for drug absorption into hepatocytes, and is the rate-limiting step in the hepatic clearance of atorvastatin[8]. Pharmacogenetic studies have mainly focused on variants of SLCO1B1 and CYP3A4/5[9,10]; however, the role of the ATP-binding cassette subfamily B member 1 (ABCB1) gene has been underexplored. ABCB1 encodes P-glycoprotein, a key efflux transporter involved in drug absorption, distribution, and elimination[11]. Its common polymorphisms, including C3435T (rs1045642), G2677T/A (rs2032582), and C1236T (rs1128503), may influence atorvastatin pharmacokinetics, treatment efficacy, and ADR risk[12].

The inter-individual variability in response to atorvastatin therapy due to genetic polymorphisms remains a significant challenge in cardiovascular pharmacotherapy. Genetic polymorphisms within ABCB1 have been proposed as key determinants of atorvastatin pharmacokinetics and clinical response. However, finding across studies have been inconsistent, with some demonstrating significant associations while others report negligible or contradictory results. A systematic review is required to clarify inconsistencies, identify knowledge gaps, assess translational potential, and inform future pharmacogenomic research direction. This review aims to systematically evaluate available evidence on ABCB1 pharmacogenetics in atorvastatin pharmacokinetics, efficacy, and adverse drug reactions. This review is expected to provide a comprehensive evidence-based assessment of the role of ABCB1 genetic variation in atorvastatin therapy. The findings will contribute to the existing body of knowledge in pharmacogenetics, support the advancement of personalised cardiovascular medicine, and potentially improve patient outcomes through more precise therapeutic strategies. This. This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD420251130481.

MATERIALS AND METHODS

Eligibility criteria

Studies will be selected according to the criteria outlined below.

a. Participants: A study needs to include one or more individuals (≥18 years) who have received atorvastatin for dyslipidemia or cardiovascular disease prevention/treatment.

b. Relevant outcome: Atorvastatin pharmacokinetics, lipid-lowering (LDC-D, Triglycerides), adverse events (myopathy, neuropathy, hepatotoxicity).

c. Study types: Either experimental or observational studies using the following designs: randomised controlled trials, cross-sectional studies, cohort studies, and case-control studies. Case reports, reviews, and editorials will be excluded.

d. Exposure: Genetic polymorphisms in ABCB1, notably C3435T, G2677T/A, and C1236T.

e. Comparators: Wild-type genotypes, other genetic variants, or different population groups.

f. Language: Studies published in English.

g. Time frame: No restrictions on publication year.

The eligibility criteria outlined above were translated into questions that were meant to facilitate the screening process (Table 1). The questions were trialled on several articles to assess their comprehensiveness and have been adapted accordingly. The answer to all questions must be 'yes' to be included in this systematic review.

Information sources and Search strategy

Potentially eligible articles will be collected from databases of PubMed/MEDLINE, Web of Science, Scopus, Hinari, and PharmGKB which are either open-access or accessible through subscriptions. Grey literature will be searched via Google Scholar and clinical trial registries. Reference lists of included studies will be screened.

Based on previous systematic reviews and consultation with a research librarian, relevant search terms were selected using combined keywords and MeSH terms for "ABCB1", "MDR1",

"polymorphism", "genetic variant", "atorvastatin", "statin", and "pharmacogenetics" (Table 2). For the query about population and lipid-lowering drugs, the search is limited to the abstract and title of the studies. The Boolean operator 'AND' was used in all of our searches.

Since the final search is expected to take place in December 2025, we set the 31st of November as the upper time limit for study inclusion. No lower limit was used since articles eligible for our systematic review are expected to be scarce. Our search terms were in English; thus, all the studies selected must be written in English.

Study records

Data management and extraction

All articles identified using the literature search strategy mentioned above will be exported as ris/.nbib files to the Zotero reference manager in a folder created for the systematic review. The primary reviewer (YOA) will screen the folder for duplicates using the "Duplicate items" in Zotero. This will be followed by importing the title and abstract into Rayyan, a free-access online programme that facilitates collaboration between multiple reviewers[13]. Both YOA and TI will screen the articles for inclusion following the process mentioned above. At the conclusion of the initial screening, the full text of the eligible articles will be imported into Zotero for the next step of the selection process. Relevant data will be extracted by YOA from the eligible articles that passed the full text stage using Excel for the following categories: (1) general study characteristics; (2) participant characteristics; (3) experiment information; (4) ABCB1 variant type; (5) atorvastatin pharmacokinetics; (6) efficacy; (7) adverse drug reaction (see Appendix A for a full overview).

Selection process

The primary reviewers (YOA and TI) will screen the title and abstract of each study that has been imported into Rayyan after the removal of duplicated articles. The screening questions (Table 2) that are based on the eligibility criteria will facilitate the screening process. Afterwards, the full reports for all the titles that scaled through the initial screening, or for which there was uncertainty, will be obtained and imported into Rayyan by YOA, while TI will screen these studies for final inclusion using the same screening questions. In the case the reviewers still disagree, a third reviewer (MBW) will be consulted to resolve the uncertainty. Reason for exclusion in the full-article stage will be recorded. The final list of included studies will be imported into Excel, and the full reports into Zotero.

Data collection process

The information from the included studies will be collected using data extraction forms (Appendix A). This form is based on several studies before protocol registration. Data extraction will be conducted by YOA in Excel, but if there is uncertainty, TI will be consulted.

Outcome prioritization

Primary outcome of interest:

The key outcome of interest is atorvastatin systemic exposure at steady state, primarily measured as the area under the plasma concentration-time curve (AUC), specifically as the mean AUC (or $AUC_{0-\infty}$/AUC_{0-t}) by ABCB1 genotype. AUC is selected as the primary outcome of interest because ABCB1 is an efflux transporter that directly affects drug absorption, distribution, and clearance (ADME), and pharmacokinetics is the most closely linked mechanistic pathway to genetic variants. Likewise, AUC is a quantitative, comparable metric across studies and is frequently reported in pharmacogenetic or pharmacokinetic studies. If AUC data are sparse, C_{max} or clearance are used as secondary pharmacokinetic measures.

Additional (secondary) outcome of interest:

1. Clinical efficacy: Absolute and percent change in LDL-C, and proportion achieving guideline LDL targets.
2. Adverse reactions/toxicity: Incidence of statin-associated myopathy (SAM), hepatotoxicity (liver enzymes elevation), peripheral neuropathy, cognitive/CNS adverse events.
3. Pharmacodynamic markers: changes in ApoB, endothelial function markers, if reported.
4. Drug-drug interactions signals: Difference in

pharmacokinetics or ADEs in the presence of known P-gp inhibitors/inducers by genotype.

5. Population genetics: Allele and haplotype frequencies across ethnic groups; test of heterogeneity by ancestry.

Risk of bias in individual studies

To evaluate the risk of bias within individual studies, the standardised critical appraisal checklist for pharmacokinetic studies and non-randomised experimental studies developed by the Joanna Briggs Institute (JBI) will be utilised[14]. The checklist examines the methodological quality of each study across the following areas using yes/no questions: (1) selected variables, (2) chosen participant groups, (3) outcome measurement, and (4) statistical analysis. Randomised controlled trials will be evaluated using the Cochrane RoB 2 tool. Discrepancies will be resolved through discussion or third-party adjudication.

Data synthesis and analysis

Where sufficient homogeneity exists, quantitative synthesis will be conducted using RevMan and R (meta/meta packages). Continuous outcomes, including AUC and LDL-C, will be expressed as mean differences or standardised mean differences with 95% confidence intervals; dichotomous outcomes, such as myopathy incidence and LDL target attainment, will be summarised using odds ratios or risk ratios.

Heterogeneity will be evaluated using I^2 statistics and Cochran's Q test. Subgroup analyses will be predetermined for ethnicity, atorvastatin dose, co-medication status, and genetic model. Publication bias will be examined with funnel plots and Egger's test when there are ≥10 studies available. The quality of the body of evidence will be graded with the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach for clinical outcomes[15].

Table 1. Screening questions were used to assess the eligibility criteria for the systematic review

Component	Question	Yes	No
Participants	Does this study at least one individual that have been prescribed atorvastatin?	Include	Exclude
Relevant outcomes	Does this study assess pharmacokinetics, lipid-lowering (LDC-D, Triglycerides), or adverse events?	Include	Exclude
Study types	Does the study report on experimental or observational study using a cross-sectional, longitudinal, or case-control study design?	Include	Exclude
Exposure	Does this study assess genetic polymorphisms in ABCB1, notably C3435T, G2677T/A, and C1236T.	Include	Exclude
Comparators	Does this study compare with wild-type genotypes, other genetic variants, or different population groups.	Include	Exclude

Table 2. Keywords used in the systematic search

SEARCH RELATING TO	KEYWORD
POPULATION AND DISEASE	African population, dyslipidaemia, cardiovascular disease, cerebral ischaemic stroke, hypertension, diabetes, metabolic syndrome.
LIPID -LOWERING DRUGS	Atorvastatin, statins
GENETIC POLYMORPHISMS	ABCB1, MDR1, P -glycoprotein,
OUTCOME	Pharmacokinetics, efficacy, adverse drug reactions, peripheral neuropathy, statin -associated myopathy (SAM)

Appendix A: Data extraction form

CATEGORY	VARIABLE	DEFINITION	EXAMPLE
IDENTIFICATION	Authors	Last name of the study authors	
	Years of publication		
	Keywords	Include keywords from the journal	
	Full Vancouver reference	Complete reference, including DOI link	
GENERAL STUDY CHARACTERISTICS	Study design	Choose the study design from the following: (a) Randomised clinical trial (b) Non-randomised experimental (c) Pharmacokinetics study (d) Other (specify)	
	Language	Language in which the study was written	
	Location	Country in which the study was conducted	
SAMPLE SIZE	Total sample size		
	Sample size per genotype		
PARTICIPANT CHARACTERISTICS	Age		
	Sex		
	BMI		
	Health status		
ABCB1 VARIANT(S) STUDIED	C3435T		
	G2677T/A		
	T1236C		
	Haplotypes		
GENOTYPING METHOD	PCR-Based methods		
	Sequencing-Based methods		
	Microarrays/Hybridisation-Based method		
	High-Resolution Melting Analysis (HRM)		
	Mass spectrometry-based Genotyping		
ALLELE / GENOTYPE FREQUENCIES			
ATORVASTATIN DOSE & REGIMEN	**Low ≤10 mg**		
	Moderate 20 mg		
	High ≥40 mg		
CO-MEDICATIONS	P-gp inhibitors		
	p-gp inducers		
PHARMACOKINETIC PARAMETERS REPORTED	AUC		
	Cmax		
	CL/F		
	$t_{1/2}$		
TIMEPOINT	Single dose		

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