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Article

Association of Pitavastatin Versus Atorvastatin Therapy With Glycaemic Control and New-Onset Diabetes in Older Adults With Atherosclerotic Cardiovascular Disease

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Abstract

Aims/Background: Statins are first-line therapy for atherosclerotic cardiovascular disease (ASCVD), but their differential effects on glucose metabolism, particularly in the elderly, remain a clinical concern. This study aimed to compare the effects of pitavastatin versus atorvastatin on glucose metabolism in elderly patients with ASCVD. **Methods**: In this retrospective cohort study conducted at Public Health Clinical Center Affiliated to Shandong University between January 2022 and December 2023, 126 elderly ASCVD patients aged ≥60 years were included and allocated to either the pitavastatin group (4 mg/day, n = 58) or the atorvastatin group (20 mg/day, n = 68). Fasting blood samples were collected at baseline and after 12 months of treatment to measure lipid profiles, glucose metabolism parameters, liver function, and renal function. **Results**: After treatment, the pitavastatin group demonstrated significantly higher levels of high-density lipoprotein cholesterol (HDL-C) (1.41 ± 0.30 mmol/L vs. 1.26 ± 0.28 mmol/L, p = 0.005). Regarding glucose metabolism, the pitavastatin group showed lower fasting plasma glucose (5.85 ± 0.70 mmol/L vs. 6.19 ± 0.85 mmol/L, p = 0.018) and glycated hemoglobin (6.10 ± 0.42% vs. 6.33 ± 0.51%, p = 0.009). No cases of new-onset diabetes were detected in the pitavastatin group, as compared to the 10.29% rate observed in the atorvastatin group. Multivariate logistic regression analysis confirmed pitavastatin as a protective factor against new-onset diabetes (odds ratio = 0.212, p = 0.018). **Conclusion**: Compared with atorvastatin, pitavastatin may be associated with better glycemic outcomes and a lower risk of new-onset diabetes in elderly ASCVD patients, supporting its consideration in clinical practice where glycemic control is a concern.

Keywords: pitavastatin; atorvastatin; glycated hemoglobin; diabetes mellitus; atherosclerosis

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of morbidity and mortality worldwide [1]. Statin therapy has been widely used to reduce cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) [2]. However, the impact of statins on glucose metabolism remains a concern, especially in elderly patients who are more prone to developing diabetes. Since different statins have varying effects on glucose control, understanding their differences is crucial to optimizing treatment strategies for elderly ASCVD patients [3,4].

Atorvastatin is one of the most commonly prescribed statins due to its efficacy in reducing LDL-C levels [5,6]. It has been shown to significantly decrease cardiovascular events in high-risk patients. A study has indicated that atorvastatin may also increase the risk of new-onset diabetes. This side effect could be particularly problematic in elderly patients, who already have a higher baseline risk for developing diabetes [7]. There is a need to explore alternative statins that offer similar cardiovascular benefits without adversely affecting glucose metabolism.

Pitavastatin is another statin that has gained attention for its lipid-lowering effects and potential advantages in glucose metabolism [8,9]. Its mechanism of action involves selective inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which might result in less disruption of insulin sensitivity compared to other statins. This makes pitavastatin an attractive option for elderly ASCVD patients who require effective lipid management while minimizing risks to glucose homeostasis [10,11].

The balance between lipid management and glucose control is critical in the treatment of elderly ASCVD patients. Dyslipidemia and impaired glucose metabolism often coexist in this population, complicating therapeutic decisions. Effective management of both conditions is essential to reduce cardiovascular risk and improve overall health outcomes. Some statins may provide better glycemic control than others, but direct comparisons between pitavastatin and atorvastatin in elderly patients are limited. In addition to their effects on lipid and glucose metabolism, statins also influence other cardiovascular risk factors, such as inflammation and endothelial function. These factors play a crucial role in the progression of atherosclerosis. By improving endothelial function and reducing inflammation, statins contribute to plaque stabilization and a reduction in cardiovascular events. The extent to which different statins

affect these parameters can vary, potentially influencing clinical outcomes [12,13,14].

Elderly patients with ASCVD face unique challenges in managing their conditions. Age-related changes in physiology and the presence of multiple comorbidities complicate treatment strategies. Moreover, elderly patients are often underrepresented in clinical trials, leading to a lack of evidence-based guidelines specifically tailored for this population. Addressing these gaps requires targeted research that focuses on understanding the specific needs and responses of elderly ASCVD patients to different statin therapies. Our research will provide valuable insights into optimizing treatment protocols and improving patient care. Enhancing our knowledge in this area will contribute to improved clinical decision-making and ultimately lead to better health outcomes for elderly patients with ASCVD.

2. Methods

2.1 Study Design and Participants

We screened elderly patients with ASCVD who were initiated on statin therapy between 1 January 2022 and 31 December 2023. This timeframe allowed for a minimum of one year of follow-up data until 31 December 2024. A total of 126 patients who met the study criteria were ultimately included.

Inclusion criteria of this study were as follows: ① age $\geq$60 years; ② a definitive diagnosis of ASCVD [15], including one or more of the following: coronary heart disease (confirmed by coronary angiography or history of myocardial infarction), ischemic cerebrovascular disease (confirmed by imaging), or peripheral arterial disease (confirmed by ultrasonography or angiography); ③ newly prescribed and continuous use of either atorvastatin or pitavastatin, with an actual medication duration of at least 11 months during the 12-month follow-up period, operationalized with no dose adjustments, no switching between statin types, no addition of other lipid-lowering agents, and no gaps in prescription refills exceeding 30 days; and ④ availability of complete baseline demographic, clinical, and laboratory data, including at least two measurements of fasting plasma glucose (FPG) and/or glycated hemoglobin (HbA1c): one at baseline (within 1 day before statin initiation) and one at the 12-month follow-up visit. Exclusion criteria were as follows: ① pre-existing diagnosis of diabetes mellitus or use of any glucose-lowering medications at baseline; ② presence of severe comorbid conditions that significantly affect glucose metabolism or life expectancy, including, but not limited to, severe hepatic insufficiency (Child–Pugh class C), end-stage renal disease (requiring dialysis), or active malignancy; ③ concomitant use of medications known to significantly influence glucose metabolism (e.g., systemic corticosteroids, potent immunosuppressants); and ④ incomplete medical records or loss to follow-up before the first post-treatment laboratory assessment.

A flowchart illustrating patient selection is shown in Fig. 1.

2.2 Group Allocation and Study Protocol

Patients were classified into an atorvastatin group (n = 68) and a pitavastatin group (n = 58) based on the initial statin prescription. Patients receiving atorvastatin (Fujian Dongrui Pharmaceutical Co., Ltd.; Putian, China; National Medicine Permit No. H20193043) at a dose of 20 mg per day were assigned to the atorvastatin group. Patients receiving pitavastatin (Nanjing Changao Pharmaceutical Co., Ltd.; Nanjing, China; National Medicine Permit No. H20203268) at a dose of 4 mg per day were assigned to the pitavastatin group. These dosing regimens were selected as they represent common, moderate-intensity starting doses in clinical practice and guidelines [16]. The index date was defined as the date of the first prescription for either statin. Baseline data were collected at the index date. Follow-up data, including lipid profiles, glucose parameters, and adverse events, were collected at the clinic visit at 12 months after the index date.

2.3 Outcome Definitions

Incidence of new-onset diabetes was defined as the occurrence of any of the following during the follow-up period: FPG $\geq$7.0 mmol/L, HbA1c $\geq$6.5%, or the initiation of any glucose-lowering medication documented for the treatment of newly diagnosed diabetes (i.e., initiated following a confirmatory laboratory result of FPG $\geq$7.0 mmol/L or HbA1c $\geq$6.5%).

Acute myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction [17] as a rise and/or a fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit, accompanied by at least one of the following: symptoms of ischemia, new ischemic electrocardiogram (ECG) changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of a coronary thrombus by angiography. Stroke was defined as an acute episode of focal or global neurological dysfunction with symptoms lasting $>$24 hours or leading to death, with imaging evidence of cerebral infarction or intracranial hemorrhage, and without evidence of a non-vascular cause. Transient ischemic attack was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction on imaging, and with clinical symptoms typically lasting $<$1 hour [18]. Coronary revascularization was defined as any percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) procedure performed during the follow-up period, as documented in the electronic medical records.

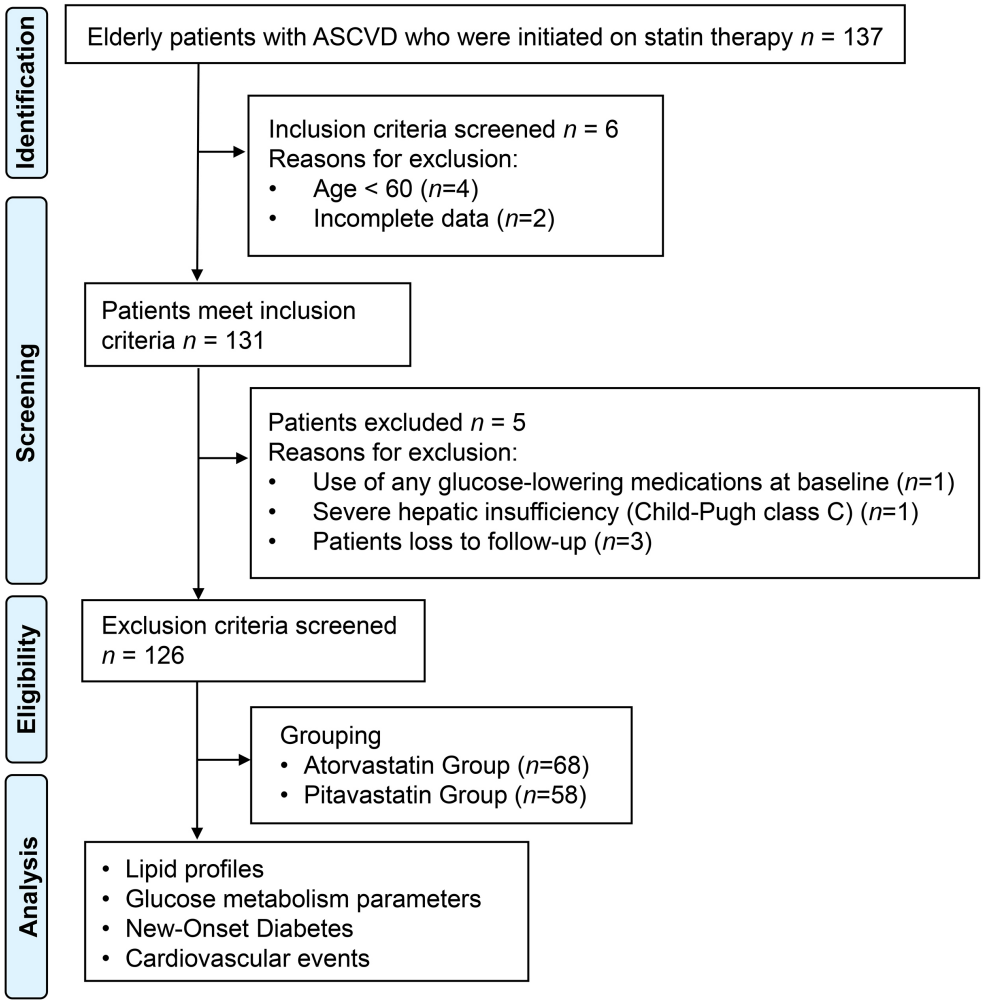

Fig. 1. Flowchart of patient selection. ASCVD, atherosclerotic cardiovascular disease.

2.4 Blood Sample and Biochemical Assays

Following an overnight fast of at least 8 hours, venous blood samples were collected from all participants. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, and creatinine were measured using standard enzymatic methods on a Mindray BS-2000M automated biochemical analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation, which incorporates age and gender. Lipid parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, apolipoprotein A1 (APO-A1), and apolipoprotein B (APO-B), were analyzed using enzymatic and immunoturbidimetric assays on the same platform. FPG was measured using the glucose oxidase method, and HbA1c was quantified by high-performance liquid chromatography (HPLC) on a Bio-Rad D-100 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

2.5 Statistical Analysis

All analyses were performed using SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). The dataset was complete with no missing values. Continuous variables were tested for normality using the Shapiro–Wilk test. As all variables met the assumption of normality, they are presented as mean ± standard deviation (SD) and were compared between the two groups using the independent samples *t*-test. For within-group comparisons of parameters before and after treatment (lipid profiles, glucose), paired samples *t*-tests were used. Categorical variables are expressed as frequencies and percentages [*n* (%)]. The standard Pearson's chi-square test was used for all categorical comparisons unless expected cell counts were below 5, in which case Fisher's exact test was applied. To identify independent factors associated with the development of new-onset diabetes, a multivariate logistic regression analysis was performed using the Firth penalized-likelihood method to correct for bias due to the small number of events. The model included the following covariates: statin treatment group (pitavastatin vs. atorvastatin), age, body mass index (BMI), gender, baseline FPG, and baseline HbA1c. These

Table 1. Comparison of baseline demographic and clinical characteristics between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	t/χ^2/Fisher	p
Age (years)	68.63 ± 2.97	68.85 ± 2.98	0.416	0.678
BMI (kg/m^2)	24.12 ± 2.31	23.95 ± 2.18	0.409	0.684
Gender (males), n (%)	49 (72.06%)	42 (72.41%)	0.002	0.965
Coronary heart disease, n (%)	47 (69.12%)	41 (70.69%)	0.037	0.848
Peripheral artery disease, n (%)	2 (2.94%)	3 (5.17%)	Fisher	0.667
Stroke history, n (%)	14 (20.59%)	10 (17.24%)	0.227	0.633
Hypertension, n (%)	50 (73.53%)	43 (74.14%)	0.006	0.938
Prior ACS (myocardial infarction or unstable angina), n (%)	15 (22.06%)	12 (20.69%)	0.035	0.852
Coronary revascularization history, n (%)	15 (22.06%)	13 (22.41%)	0.002	0.962
Use of anti-hypertensive agents, n (%)				
- ACEIs and/or ARBs	34 (50.00%)	32 (55.17%)	0.336	0.562
- Calcium channel blocker	32 (47.06%)	26 (44.83%)	0.063	0.802
- Diuretics	13 (19.12%)	10 (17.24%)	0.074	0.786
- β receptor antagonist	25 (36.76%)	22 (37.93%)	0.018	0.893
Use of anti-platelet agents, n (%)	43 (63.24%)	38 (65.52%)	0.071	0.790
Use of warfarin, n (%)	6 (8.82%)	6 (10.34%)	0.084	0.772

ACEIs, angiotensin converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index.

covariates were selected based on clinical relevance and prior literature demonstrating their association with new-onset diabetes in statin-treated populations, while also considering the limited number of outcome events to avoid model overfitting. Prior to multivariate logistic regression, multicollinearity among covariates was assessed using variance inflation factor (VIF) and tolerance statistics. All VIF values were below 2.0 (tolerance $>$ 0.5), indicating no significant multicollinearity. A two-tailed p-value of $<$0.05 was considered statistically significant for all analyses.

3. Results

3.1 Baseline Characteristics

The comparison of the baseline demographic and clinical characteristics between the atorvastatin group and the pitavastatin group (Table 1) revealed no significant differences. There were no significant differences in age (p = 0.678), BMI (p = 0.684), gender distribution (p = 0.965), coronary heart disease (p = 0.848), peripheral artery disease (p = 0.667), stroke history (p = 0.633), hypertension (p = 0.938), prior myocardial infarction or unstable angina (p = 0.852), coronary revascularization history (p = 0.962), the use of anti-hypertensive agents (angiotensin converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs]: p = 0.562, calcium channel blocker: p = 0.802, diuretics: p = 0.786, β receptor antagonist: p = 0.893), the use of anti-platelet agents (p = 0.790), or warfarin use (p = 0.772).

There were no significant differences in the baseline clinical and laboratory parameters between the atorvastatin group and the pitavastatin group (Table 2), including systolic blood pressure (SBP) (p = 0.789), diastolic blood pressure (DBP) (p = 0.879), heart rate (p = 0.751), respiratory rate (p = 0.481), AST (p = 0.241), ALT (p = 0.439), uric acid (p = 0.681), creatinine (p = 0.755), or eGFR (p = 0.678).

3.2 Changes in Lipid Profiles

In the comparison of lipid profiles at baseline between the atorvastatin group and the pitavastatin group (Table 3), no significant differences were observed across any of the parameters. There were no significant differences in TC (p = 0.750), TG (p = 0.802), HDL-C (p = 0.387), LDL-C (p = 0.534), APO-A1 (p = 0.331), or APO-B (p = 0.755).

After statin treatment, the pitavastatin group showed significantly higher HDL-C levels (1.41 ± 0.30 vs. 1.26 ± 0.28, t = 2.882, p = 0.005) compared with the atorvastatin group (Table 4). No significant differences were found for TC, TG, LDL-C, APO-A1, or APO-B ($p > 0.05$). Within-group comparisons revealed that TC, LDL-C, and APO-B significantly decreased from baseline in the atorvastatin group, while TC, LDL-C, HDL-C, and APO-B showed significant changes in the pitavastatin group ($p < 0.001$).

3.3 Changes in Fasting Plasma Glucose and Glycated Hemoglobin

There were no significant differences in baseline FPG and baseline HbA1c between the atorvastatin group and the pitavastatin group ($p > 0.05$) (Table 5). After statin treatment, the pitavastatin group showed significantly lower FPG (5.85 ± 0.70 vs. 6.19 ± 0.85, t = 2.401, p = 0.018) and HbA1c (6.10 ± 0.42 vs. 6.33 ± 0.51, t = 2.654, p = 0.009), compared to the atorvastatin group. The atorvastatin group showed a significant increase in both FPG and HbA1c compared to their baseline levels ($p < 0.001$), whereas no significant within-group changes were observed for these parameters in the pitavastatin group ($p > 0.05$).

Table 2. Comparison of baseline clinical and laboratory parameters between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	t	p
SBP (mmHg)	128.45 ± 12.11	127.88 ± 11.75	0.268	0.789
DBP (mmHg)	77.12 ± 8.74	76.89 ± 8.41	0.152	0.879
Heart rate (times per minute)	72.35 ± 9.01	71.84 ± 8.67	0.319	0.751
Respiratory rate (times per minute)	18.15 ± 1.41	17.96 ± 1.58	0.707	0.481
AST (IU/L)	24.12 ± 4.89	25.13 ± 4.67	1.178	0.241
ALT (IU/L)	24.56 ± 4.23	25.18 ± 4.75	0.777	0.439
Uric acid (mg/dL)	5.48 ± 1.02	5.41 ± 1.03	0.412	0.681
Creatinine (mg/dL)	0.82 ± 0.19	0.81 ± 0.23	0.313	0.755
eGFR (mL/minute/1.73 m^2)	78.22 ± 12.45	79.13 ± 11.86	0.416	0.678

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Table 3. Comparison of lipid profiles at baseline between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	t	p
TC (mmol/L)	4.28 ± 0.47	4.25 ± 0.46	0.320	0.750
TG (mmol/L)	1.62 ± 0.58	1.65 ± 0.69	0.251	0.802
HDL-C (mmol/L)	1.23 ± 0.25	1.27 ± 0.29	0.869	0.387
LDL-C (mmol/L)	2.58 ± 0.32	2.55 ± 0.33	0.624	0.534
APO-A1 (g/L)	1.36 ± 0.20	1.40 ± 0.22	0.977	0.331
APO-B (g/L)	0.88 ± 0.12	0.89 ± 0.10	0.312	0.755

APO-A1, apolipoprotein A1; APO-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 4. Comparison of lipid profiles after statin treatment between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	t	p
TC (mmol/L)	3.55 ± 0.40*	3.62 ± 0.43*	1.001	0.319
TG (mmol/L)	1.45 ± 0.55	1.48 ± 0.53	0.340	0.735
HDL-C (mmol/L)	1.26 ± 0.28	1.41 ± 0.30*	2.882	0.005
LDL-C (mmol/L)	2.21 ± 0.38*	2.25 ± 0.41*	0.592	0.555
APO-A1 (g/L)	1.39 ± 0.22	1.43 ± 0.24	0.958	0.340
APO-B (g/L)	0.79 ± 0.10*	0.81 ± 0.11*	0.831	0.408

Note: * $p < 0.001$ compared to baseline after statin treatment.

APO-A1, apolipoprotein A1; APO-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

3.4 Incidence of New-Onset Diabetes

Regarding diabetes incidence, the atorvastatin group had a significantly higher incidence of new-onset diabetes than the pitavastatin group (10.29% vs. 0%, $p = 0.014$) (Table 6).

3.5 Cardiovascular Events

There were no significant differences in the incidence of cardiovascular events, such as acute myocardial infarction (nonfatal) ($p = 0.441$), ischemic stroke (nonfatal) ($p = 0.502$), or transient ischemic attack ($p = 1.000$), between the atorvastatin and pitavastatin groups (Table 7). The atorvastatin group had a significantly higher incidence of coronary revascularization (16.18% vs. 3.45%, $\chi^2 = 5.480$, $p = 0.019$).

3.6 Multivariate Logistic Regression Analysis

In the multivariable analysis of new-onset diabetes using Firth's bias-corrected logistic regression (Table 8), pitavastatin treatment remained an independent protective factor (adjusted $p = 0.018$, odds ratio [OR] = 0.212, 95% confidence interval [CI] = 0.066–0.724). Among the other covariates, higher baseline HbA1c was significantly associated with an increased risk of new-onset diabetes (adjusted $p = 0.032$). Age, BMI, gender, and baseline FPG were not significantly associated with new-onset diabetes in this model (all $p > 0.05$).

4. Discussion

Statin therapy is a cornerstone in the management of ASCVD, but its impact on glucose metabolism remains a concern, particularly in elderly patients. This study aimed

Table 5. Comparison of FPG and HbA1c between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	t	p
FPG (mmol/L)				
- Baseline	5.82 ± 0.59	5.79 ± 0.61	0.262	0.793
- After statin treatment	6.19 ± 0.85*	5.85 ± 0.70	2.401	0.018
HbA1c (%)				
- Baseline	5.99 ± 0.62	5.96 ± 0.59	0.280	0.780
- After statin treatment	6.33 ± 0.51*	6.10 ± 0.42	2.654	0.009

Note: * $p < 0.001$ compared to baseline after statin treatment.

FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

Table 6. Comparison of incidence of new-onset diabetes between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	Fisher	p
Incidence of new-onset diabetes, n (%)	7 (10.29%)	0 (0%)	Fisher	0.014

Table 7. Comparison of cardiovascular events between the atorvastatin and pitavastatin groups.

Parameters	Atorvastatin group (n = 68)	Pitavastatin group (n = 58)	χ^2/Fisher	p
Acute myocardial infarction (nonfatal), n (%)	5 (7.35%)	2 (3.45%)	Fisher	0.441
Ischemic stroke (nonfatal), n (%)	2 (2.94%)	0 (0%)	Fisher	0.502
Transient ischemic attack, n (%)	1 (1.47%)	0 (0%)	Fisher	1.000
Coronary revascularization, n (%)	11 (16.18%)	2 (3.45%)	5.480	0.019

Table 8. Multivariate logistic regression analysis of new-onset diabetes.

Parameters	β	SE	p	OR	95% CI
Pitavastatin treatment	−1.561	0.661	0.018	0.212	0.066–0.724
Age	0.041	0.038	0.280	1.044	0.975–1.124
BMI	0.095	0.071	0.181	1.107	0.964–1.266
Gender (males)	0.255	0.481	0.595	1.294	0.504–3.317
Baseline FPG	0.422	0.265	0.111	1.524	0.913–2.566
Baseline HbA1c	0.918	0.428	0.032	2.502	1.086–5.781

BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OR, odds ratio; SE, standard error.

to compare the effects of pitavastatin and atorvastatin on glucose metabolism in elderly ASCVD patients. Our findings suggest that pitavastatin may offer certain advantages over atorvastatin in terms of glucose control and lipid profile improvements.

After statin treatment, both groups showed improvements in their lipid profiles. The reductions in key atherogenic lipids, including LDL-C, total cholesterol, and apolipoprotein B, were comparable between the pitavastatin and atorvastatin groups. This indicates that both statin regimens provided equivalent efficacy in achieving the primary lipid-lowering goal for ASCVD risk reduction. The comparable effects on LDL-C, a primary target in lipid management, suggest that the choice between these two statins may not compromise the fundamental cardiovascular protective benefit derived from lipid lowering [9,19]. The pitavastatin group, however, exhibited higher levels of HDL-C compared to the atorvastatin group. HDL-C is known for its protective role against cardiovascular diseases by promoting reverse cholesterol transport and reducing inflammation. The mechanism behind this difference could be related to the unique pharmacological properties of pitavastatin, which might have a more favorable effect on high-density lipoprotein (HDL) metabolism. Although the exact mechanism underlying the greater increase in HDL-C with pitavastatin remains to be fully elucidated, our findings of a significantly higher HDL-C level are consistent with prior observations that pitavastatin may exert a more favorable effect on HDL metabolism compared with atorvastatin [9,20].

The observed relative reduction in LDL-C in our study appears modest compared to the typical ~30% expected from moderate-intensity statins in clinical trial settings. This discrepancy may be attributed to several factors inherent to our real-world, elderly cohort. The baseline LDL-C levels in our patients were already relatively low, potentially reflecting prior lifestyle interventions or less severe dyslipidemia, leaving less absolute room for reduction. Real-world medication adherence may not match the perfect compliance seen in controlled trials. The selected

moderate dose represents a common starting point in elderly patients for safety, and some individuals may have a diminished pharmacodynamic response. Nonetheless, both groups achieved significant within-group LDL-C reductions, and the comparable inter-group reduction suggests equivalent lipid-lowering efficacy between the two statins at the doses used, which is the primary comparative objective of this analysis.

One of the most striking differences observed was the change in FPG and HbA1c levels after statin treatment. Patients in the pitavastatin group experienced lower levels of FPG and HbA1c compared to those in the atorvastatin group. This finding is important because it indicates that pitavastatin may have a lesser adverse effect on glucose metabolism than atorvastatin. The underlying mechanism could involve the differential impact of these statins on insulin sensitivity and pancreatic beta-cell function, which are central to the regulation of glucose homeostasis [21,22]. Atorvastatin has been associated with reduced insulin sensitivity and impaired beta-cell function, possibly due to its greater potency in inhibiting HMG-CoA reductase, leading to increased intracellular cholesterol levels and subsequent alterations in insulin signaling pathways [23]. In contrast, pitavastatin's relatively weaker inhibition of HMG-CoA reductase might result in less disruption of insulin action, thereby preserving better glucose homeostasis [24,25]. Thus, the differential effects on these core mechanisms of glucose metabolism may account for the observed clinical outcomes.

The incidence of new-onset diabetes was notably lower in the pitavastatin group compared to the atorvastatin group. This aligns with previous studies suggesting that the use of different statins imposes varying risks for diabetes [26]. For instance, a recent individual participant data meta-analysis of large-scale randomized trials by the Cholesterol Treatment Trialists' (CTT) Collaboration [27] confirmed that statin therapy, particularly more intensive regimens often incorporating high-dose atorvastatin, is associated with a dose-dependent increased risk of new-onset diabetes. The mechanism behind this increased risk involves multiple factors, including statin-induced reduction in insulin secretion and impairment of insulin sensitivity. Pitavastatin, however, appears to have a lower propensity to cause these adverse metabolic effects, likely due to its distinct pharmacokinetic and pharmacodynamic properties. These include a more selective inhibition of HMG-CoA reductase in liver cells and a minimal impact on peripheral tissues, which are crucial for maintaining normal glucose metabolism [9]. Our findings, which demonstrate a markedly lower incidence of new-onset diabetes with pitavastatin, are strongly supported by a recent systematic review and meta-analysis by Singh et al. [28], which concluded that pitavastatin was associated with a significantly lower risk of new-onset diabetes mellitus compared to atorvastatin. The consistency between their pooled results and our single-center data in a high-risk elderly population reinforces the reliability of the conclusion that pitavastatin is associated with a more favorable glycemic profile.

The observation of zero new-onset diabetes events in the pitavastatin group in the present study, while striking, should be interpreted with caution. It may reflect the drug's favorable glycemic profile, the relatively short 12-month follow-up, and the limited sample size, which could underestimate the true incidence. Longer-term studies with larger cohorts are warranted to confirm this observation.

In terms of cardiovascular events, the atorvastatin group had a higher incidence of coronary revascularization. It is important to note that this observation is not isolated. The randomized trial by Moroi et al. [29], which compared pitavastatin and atorvastatin in high-risk patients, also reported a numerical difference favoring pitavastatin for a composite endpoint that included clinically indicated coronary revascularization, despite similar achieved LDL-C levels between groups. Our real-world data thus echo a pattern observed in a prior controlled setting. Importantly, as an observational study, our analysis cannot establish causality or elucidate the underlying mechanism for this difference, which may relate to unmeasured confounding factors (e.g., baseline plaque burden, symptom severity) or non-lipid pleiotropic effects. Therefore, this finding should be interpreted as hypothesis-generating and underscores the need for further investigation into potential outcome differences between these statins beyond lipid parameters [10,30,31].

It is important to interpret these findings on cardiovascular events with caution. The small sample size and the consequently low number of observed events (e.g., only 7 total nonfatal myocardial infarctions, 2 strokes) substantially limit the statistical power to identify differences between groups. Therefore, the observed numerical differences, including the higher revascularization rate in the atorvastatin group, should be considered exploratory and hypothesis-generating rather than conclusive. They highlight the need for verification in larger, adequately powered studies.

Multivariate analysis using a bias-corrected method (Firth's regression) identified pitavastatin treatment as an independent protective factor against new-onset diabetes, even after adjusting for baseline glucose metabolism. As expected, a higher baseline HbA1c was a significant risk factor for developing diabetes. This underscores the importance of considering both the type of statin and the patient's pre-existing glycemic status when managing ASCVD in elderly patients at higher metabolic risk. The protective effect of pitavastatin against diabetes could be multifactorial, involving both direct effects on glucose metabolism and indirect effects through modulation of lipid profiles and inflammatory markers.

While a previous study has compared the metabolic effects of pitavastatin and atorvastatin in broader populations, including patients with established diabetes or prediabetes [9], our study specifically addresses a critical, understud-

ied, and high-risk demographic: elderly patients with established ASCVD but without baseline diabetes. This population is particularly vulnerable to the diabetogenic effects of statins due to age-related metabolic changes and polypharmacy. Furthermore, unlike many prior randomized trials, our real-world, retrospective design provides insights into the comparative effectiveness of these statins under conditions of routine clinical practice, which may enhance the generalizability of our findings to typical elderly ASCVD management.

Unlike previous studies that often included mixed-age populations or patients with pre-existing diabetes, our study specifically enrolled elderly ASCVD patients without baseline diabetes—a group particularly vulnerable to statin-induced glycemic deterioration. Furthermore, while prior research has compared statin effects on lipid profiles, our 12-month follow-up design with comprehensive glycemic endpoints, including FPG, HbA1c, and incident diabetes, provides real-world evidence on the comparative metabolic safety of pitavastatin versus atorvastatin in this high-risk elderly population. These distinctions underscore the unique contribution of our findings to the existing literature and address a critical evidence gap in the management of elderly ASCVD patients.

Despite the promising results, this study has several limitations. The sample size was modest, which may limit the statistical power to detect differences in infrequent endpoints and increase the susceptibility to chance findings. It was a non-random, retrospective analysis, which may introduce biases and confounding factors. The modest sample size and non-randomized design are important limitations that preclude definitive conclusions and underscore the need for large-scale, multicenter randomized controlled trials to confirm our observations. The small number of new-onset diabetes events, despite the use of a bias-corrected statistical model, limits the precision of our multivariate analysis and precludes the adjustment for a wider set of potential confounders. The follow-up period was limited to one year, which may not be sufficient to fully capture long-term outcomes. Longer-term studies are needed to assess the sustained effects of pitavastatin on glucose metabolism and cardiovascular outcomes. Since our study focused on elderly ASCVD patients, future research should explore whether these findings can be generalized to younger populations or those with different types of cardiovascular diseases. While our clinical data demonstrate differences in HDL-C and glycemic outcomes, it is important to note that the discussions regarding potential mediating mechanisms (e.g., cholesterol ester transfer protein [CETP] activity, insulin sensitivity) are speculative and based on extrapolation from prior mechanistic and preclinical studies, as these specific biomarkers were not measured in our present clinical cohort. Additionally, the single follow-up assessment at 12 months may not capture earlier metabolic changes, as statin-related alterations in glucose metabolism can occur within 3–6 months. Future studies with multiple interim assessments are warranted to better characterize glycemic changes over a defined timeline. The combination of a modest sample size and a retrospective design necessitates cautious interpretation of findings, and they should be viewed as hypothesis-generating for future large-scale, prospective investigations.

Our study suggests that pitavastatin may offer advantages over atorvastatin in terms of glucose metabolism and lipid profile improvements in elderly ASCVD patients. The mechanisms underlying these differences likely involve the unique pharmacological properties of pitavastatin, which appear to have a lesser impact on insulin sensitivity and a more favorable effect on HDL-C levels. These findings highlight the importance of selecting the appropriate statin based on individual patient characteristics and risk factors. Further research is warranted to confirm these observations and to explore the broader implications of these findings in clinical practice. Enhancing our understanding of the differential effects of various statins will ultimately contribute to better patient care and improved outcomes in the management of ASCVD.

5. Conclusion

This study suggests that pitavastatin may have potential advantages over atorvastatin in terms of glucose metabolism and lipid profile improvements in elderly patients with ASCVD. Pitavastatin may provide improved control of FPG and HbA1c levels, potentially reducing the risk of new-onset diabetes. Pitavastatin treatment was associated with higher HDL-C levels, indicating possible benefits in overall lipid balance. These findings imply that pitavastatin might be a preferable option for elderly ASCVD patients, particularly those at risk of developing diabetes. Given the modest sample size, retrospective design, and the relatively short 12-month follow-up period, our findings should be interpreted as preliminary and validated through long-term prospective studies with larger cohorts and extended follow-up.

Key Points

• In this retrospective study of elderly atherosclerotic cardiovascular disease (ASCVD) patients without baseline diabetes, pitavastatin (4 mg/day) was associated with more favorable glycemic outcomes compared to atorvastatin (20 mg/day), including lower fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels after 12 months of treatment.

• New-onset diabetes was not observed in the pitavastatin group (0%), whereas it occurred in 10.29% of patients in the atorvastatin group, and pitavastatin treatment remained an independent protective factor against new-onset diabetes in a bias-corrected multivariate analysis.

• Pitavastatin therapy led to a significantly greater increase in high-density lipoprotein cholesterol (HDL-C) levels compared to atorvastatin, suggesting an additional ben-

efit on the lipid profile beyond comparable reductions in atherogenic lipids

• The findings suggest that in elderly ASCVD patients where glycemic control is a concern, pitavastatin may offer a therapeutic advantage over atorvastatin by providing effective lipid management with a lower risk of worsening glucose metabolism.

Availability of Data and Materials

The data that support the findings of this study are available from the first author upon reasonable request.

Author Contributions

HWL drafted the initial version. HWL and JL designed the research study. HWL and JL performed the research. HWL analyzed the data. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This single-center, retrospective cohort study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board and Ethics Committee of Public Health Clinical Center Affiliated to Shandong University (Approval Number: GWLCZXEC-SOP-K-2025-183). The requirement for informed consent was waived due to the retrospective nature of the analysis, which utilized exclusively de-identified patient data extracted from the electronic medical record system.

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Conflict of Interest

The authors declare no conflict of interest.

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