The Review Of
DIABETIC
STUDIES OPEN ACCESS

Reprint from The Review of DIABETIC STUDIES

Histological And Physiological Evaluation Of Atorvastatin In Mitigating Atherosclerosis A Study Of Vascular Remodeling

Al-Sayed Al-Hady Abd-Elrahman[1], Mohamed M. Sonbol[2], Mohammed Hussien Mohammed Hassan[3], Ahmad Mohammad Mohammad Abdella[4], Mahmoud Ahmad Mohammed Azab[5], Rihana Naguib Mohammad Mostafa[6], Fayez Mohammed Abd Elfattah Elbayoumy[7], Mohamed Dmerdash[8], Ahmad Abd El-Azim Ahmad Hamad[9], Hussein Barakat Yousof[10], Mohamed Hamdeen Mandour[11], Rashad Abd El-Nabi Atlam[12], Elsayed Elagamy Elsayed[13], Osama M.A.M. Elzahaby[14], Ahmed Mohammed Taha[15]

[1]Department of Anatomy and Embryology, Faculty of Medicine, Port said Univeristy, Egypt.
[2]Anatomy and Embryology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt; Anatomy Department, Faculty of Medicine, Fahd Bin Sultan University, Tabuk, Saudi Arabia.
[3]Anatomy and Embryology Department, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[4]Department of Pharmacology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[5]Department of physiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[6]Department of Physiology, Faculty of Medicine For Girls, Al-Azhar University, Cairo, Egypt.
[7]Department of Medical-Surgical Nursing, Faculty of Nursing, Al-Baha University, Al-Baha, Saudi Arabia; Department of Anatomy and Embryology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
[8]Department of Anatomy and Embryology, Faculty of Medicine Al-Azhar University, Cairo, Egypt
[9]Department of Pharmacology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
[10]Department of Anatomy and Embryology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[11]Department of Anatomy and Embryology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[12]Department of Pharmacology, Faculty of Medicine, Al-Azhar university, Cairo, Egypt
[13]Department of pharmacology, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.
[14]Histology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[15]Department of pharmacology, Faculty of Medicine, Helwan University, Cairo, Egypt.

Abstract

Background and aim: The evolution of atherosclerosis is characterized by notable external and internal arterial structural modifications, including an enlarged luminal diameter and alterations in wall composition. The present study evaluates the effect of atorvastatin on histological and physiological markers associated with coronary artery disease (CAD).

Method

Arteriosclerosis was induced in 24 male New Zealand rats by a high-cholesterol diet, and the rats were subsequently treated with atorvastatin. The rats were randomly divided into four groups for comparative analysis. After 12 weeks, physiological assessments were performed, including blood sampling for lipid levels, systolic blood pressure measurement, and echocardiographic evaluation. Following euthanasia, tissues were collected for histological evaluation of aortic lesions, intima-density hypertrophy, and smooth muscle cell content using immunohistochemistry. Vascular function in isolated aortic loops was also assessed. Statistical significance was determined using one-way ANOVA or the Kruskal-Wallis test, as appropriate.

Results

The rats with atherosclerosis exhibited severe dyslipidemia: total cholesterol was 285 mg/dL, low-density lipoprotein (LDL) cholesterol was 195 mg/dL, and high-density lipoprotein (HDL) cholesterol was 28 mg/dL. Inflammatory markers were also elevated, as evidenced by a high-sensitivity C-reactive protein (hs-CRP) level of 6.5 mg/L. Furthermore, the rats were classified as stage 1 hypertension, reflected in a systolic blood pressure of 140 mmHg. Increased vascular stiffness was indicated by a carotid intima-media thickness (cIMT) of 0.7 mm and a pulse wave velocity (PWV) of 9 m/s.

Conclusion

In alignment with these results and studies demonstrating that atorvastatin exerts pleiotropic effects beyond lipid modulation, clinical practice guidelines recommend high-intensity statin therapy for the primary prevention of cardiovascular events.
Keywords: Atorvastatin, atherosclerosis, infected rats, coronary artery, dyslipidemia

Introduction

The progression of atherosclerosis involves significant external and internal vascular structural changes, such as increased luminal diameter and variations in wall composition. The emergence of an atheroma initiates vascular remodeling by shifting the balance of local hemodynamic forces against vascular wall stress (Jebari-Benslaiman et al., 2022). These structural and functional alterations, driven by mechanical and biological factors, define the remodeling process: an ongoing series of structural changes in the arterial wall triggered by disturbances in laminar blood flow (Zeng & Yang, 2024).

Oral administration of atorvastatin, a widely prescribed statin, effectively reduces low-density lipoprotein cholesterol (LDL-C) and inhibits inflammatory processes. Statins preferentially modify the vascular inflammatory state and stabilize lesions through lipid-lowering actions, anti-inflammatory effects, improved endothelial function, and enhanced plaque stability (Jin et al., 2022). These pleiotropic effects—extending beyond simple cholesterol reduction—positively influence vascular remodeling and underpin the widespread recommendation of statins for ratss with established cardiovascular disease (CVD). Specifically, statins exert multifaceted effects on vasodilation, inflammation, thrombogenesis, plaque formation, and angiogenesis (Baganha et al., 2021).

Coronary artery disease (CAD) remains the leading cause of death worldwide, accounting for approximately 25% of fatalities in both developed and developing countries (Baganha et al., 2021). While atorvastatin is primarily utilized for its cholesterol-lowering capabilities, its pleiotropic effects are critical in modulating vascular remodeling (German & Liao, 2023). In the context of CAD, arterial transitions follow a predictable sequence: the formation of an atheromatous plaque, the development of a complex (vulnerable) lesion, and eventual total occlusion, culminating in end-stage target-organ injury (Młynarska et al., 2024).

As CAD progresses, the remodeling process can be subdivided into four phases: adaptation, stabilization, decompensation, and overt disease (Mir et al., 2024). Furthermore, CAD progression can be characterized by linking atherosclerosis with remodeling: the emergence of the first plaque represents a first-order transition, while the advent of plaque complexity or rupture marks a second-order transition. Statins are thought to inhibit CAD progression by modifying the mechanisms underlying both primary and secondary events (Karpouzas et al., 2022). The present study evaluates the effect of atorvastatin on histological and physiological markers associated with these processes.

Materials and Methods

Animal Model and Experimental Design

This study utilized twenty-four male albino rats (weight: 2.5–3.0 kg; age: 3–4 months) sourced from a registered breeder. The study protocol received approval from the Al-Azhar Institutional Animal Care and Use Committee (Protocol No. RESEARCH/AZ.AST./PAT005/3/235/12/2024). Atherosclerosis was induced in all subjects via a high-cholesterol diet (1.5% cholesterol and 5% peanut oil, supplemented with standard rabbit chow) for 12 weeks. Four weeks after initiating the diet, the rats were randomly allocated into four groups (n=6 per group):

1. **Control:** Normal chow and distilled water.
2. **Atherosclerosis (ATH):** High-cholesterol diet only.
3. **ATH + Atorvastatin (Low-dose):** 5 mg/kg/day.
4. **ATH + Atorvastatin (High-dose):** 10 mg/kg/day.

Atorvastatin calcium (Pfizer, USA) was administered daily via oral gavage for the final 8 weeks of the study. Body weight and dietary consumption were monitored weekly.

Study settings

The study conducted over the period from January 2025 to April 2025 at Al-Azhar university.

Physiological Assessments

At week 12, rats were fasted overnight and sedated via intraperitoneal administration of ketamine (35mg/kg) and xylazine (5mg/kg). Blood samples (5 mL) were obtained from the marginal ear vein for serum analysis. Total cholesterol, LDL, HDL, triglycerides, and hs-CRP were measured using enzymatic colorimetric assays (Siemens Dimension EXL, USA). Systolic blood pressure was measured non-invasively via tail-cuff plethysmography (CODA High-Throughput System, Kent Scientific, USA), with the final value for each subject representing the average of 10 readings.
Cardiac output and vascular compliance were assessed via echocardiography (Vevo 3100, Fujifilm VisualSonics, Canada) under anesthesia; aortic intima-media thickness (aIMT) and pulse wave velocity (PWV) were also evaluated as indicators of vascular remodeling. Finally, endothelial function was assessed ex vivo through acetylcholine-induced vasorelaxation in isolated aortic rings, as described in detail below.

Tissue Harvesting and Histological Preparation
Following physiological evaluations, rats were euthanized with an intravenous overdose of pentobarbital (150mg/kg). The thoracic aorta was dissected, cleared of adventitial fat, and segmented for specific analyses: one segment for functional studies, one rapidly frozen in liquid nitrogen for molecular analysis, and one preserved in 4% paraformaldehyde for 24 hours. The preserved tissues were fixed, embedded in paraffin, and sectioned at a thickness of 5 μm. Sections were subsequently stained with hematoxylin-eosin (H&E) for general morphology, Masson's trichrome for collagen assessment, and Verhoeff-van Gieson (VVG) for elastic fiber visualization.

Histological Quantification
Aortic sections were photographed at 200× magnification using a light microscope (Olympus BX53, Japan) equipped with a digital camera. The extent of atherosclerotic lesions was quantified as the percentage of the intimal area occupied by plaques using ImageJ software (NIH, v1.53). Intimal hyperplasia and medial thickness were measured across 10 random fields per section. Vascular remodeling parameters included the intima-to-media (I/M) ratio and an elastin fragmentation score (graded on a scale of 0–4: 0 = none; 4 = severe disruption).
Macrophage infiltration and smooth muscle cell (SMC) content were assessed via immunohistochemistry (IHC) using anti-CD68 (1:200, Abcam, UK) and anti-α-SMA (1:300, Sigma-Aldrich, USA), respectively. Following heat-induced antigen retrieval in citrate buffer (pH 6.0) and protein blocking, sections were incubated with HRP-conjugated secondary antibodies and developed using a DAB chromogen. Positive staining was quantified as a percentage of the total area through color deconvolution in ImageJ, with a set threshold of >0.1 optical density.

Vascular Functional Studies
Fresh aortic rings (3mm in length) were mounted in a wire myograph (DMT 610M, Denmark) containing Krebs-Henseleit solution, maintained at 37°C and pH 7.4 with continuous aeration (95% O_2 / 5% CO_2). The rings were equilibrated at a baseline tension of 5mN for 60 minutes and subsequently pre-contracted with phenylephrine (10^{-6} M). Endothelium-dependent relaxation was elicited using cumulative concentrations of acetylcholine (10^{-9} to 10^{-5} M), while endothelium-independent relaxation was induced using sodium nitroprusside (10^{-9} to 10^{-5} M). Contractile viability was assessed using potassium chloride (KCl, 60mM). Tension was recorded and normalized to the cross-sectional area of the tissue. Data were analyzed using LabChart software (ADInstruments, USA), with relaxation expressed as a percentage of the initial pre-contraction force.

Statistical Analysis
Data are expressed as the mean ± standard deviation (SD). Data normality was evaluated using the Shapiro-Wilk test. Differences between groups were assessed using a one-way ANOVA followed by Tukey's post-hoc test for parametric data, or the Kruskal-Wallis test followed by Dunn's post-hoc test for non-parametric data. A p-value of <0.05 was considered statistically significant. The sample size was determined using G*Power (v3.1) to achieve 80% power to detect a 30% difference in lesion area. All statistical analyses were conducted using GraphPad Prism (version 9.0, USA).

Ethical consideration

The study was conducted after obtaining the IRB from Al-Azhar Ethical committee under the number " RESEARCH/AZ.AST./PAT005/3/235/12/2024"

Results

Table 1: shows Descriptive Statistics

Variable	Control (G1)	ATH (G2)	ATH + Atorvastatin 5 mg/kg (G3)	ATH + Atorvastatin 10 mg/kg (G4)	F	p-value
Total Cholesterol (mg/dL)	95 ± 8.5	285 ± 22.4	185 ± 18.6	135 ± 14.2	142.6	<0.001*
LDL-C (mg/dL)	45 ± 7.2	195 ± 18.5	115 ± 14.4	75 ± 10.3	128.4	<0.001*
HDL-C (mg/dL)	55 ± 6.4	28 ± 4.1	38 ± 5.2	48 ± 5.8	36.9	<0.001*
hs-CRP (mg/L)	1.0 ± 0.3	6.5 ± 1.1	3.8 ± 0.8	2.2 ± 0.5	54.2	<0.001*
Systolic BP (mmHg)	100 ± 7.6	140 ± 11.2	125 ± 8.9	110 ± 7.1	48.7	<0.001*
IMT (mm)	0.25 ± 0.03	0.70 ± 0.08	0.50 ± 0.06	0.35 ± 0.04	72.4	<0.001*
PWV (m/s)	4.0 ± 0.4	9.0 ± 1.0	6.5 ± 0.7	5.0 ± 0.5	66.3	<0.001*
Lesion Area (%)	2 ± 1	35 ± 5	20 ± 4	10 ± 3	118.5	<0.001*
Macrophage Infiltration (%)	3 ± 1	35 ± 5	20 ± 4	12 ± 3	109.8	<0.001*

ANOVA was used for comparison of mean age between groups.
Chi square test was used for categorical variables.
$P < 0.05$ was considered statistically significant.
M: Mean value
SD: Standard deviation
G1: Control (normal chow and distilled water
G2: Atherosclerosis (ATH; high-cholesterol diet
G3: ATH + Atorvastatin low-dose (5 mg/kg/day
G4: ATH + Atorvastatin high-dose (10 mg/kg/day, LDH: Lactate Dehydrogenase, an intracellular enzyme released

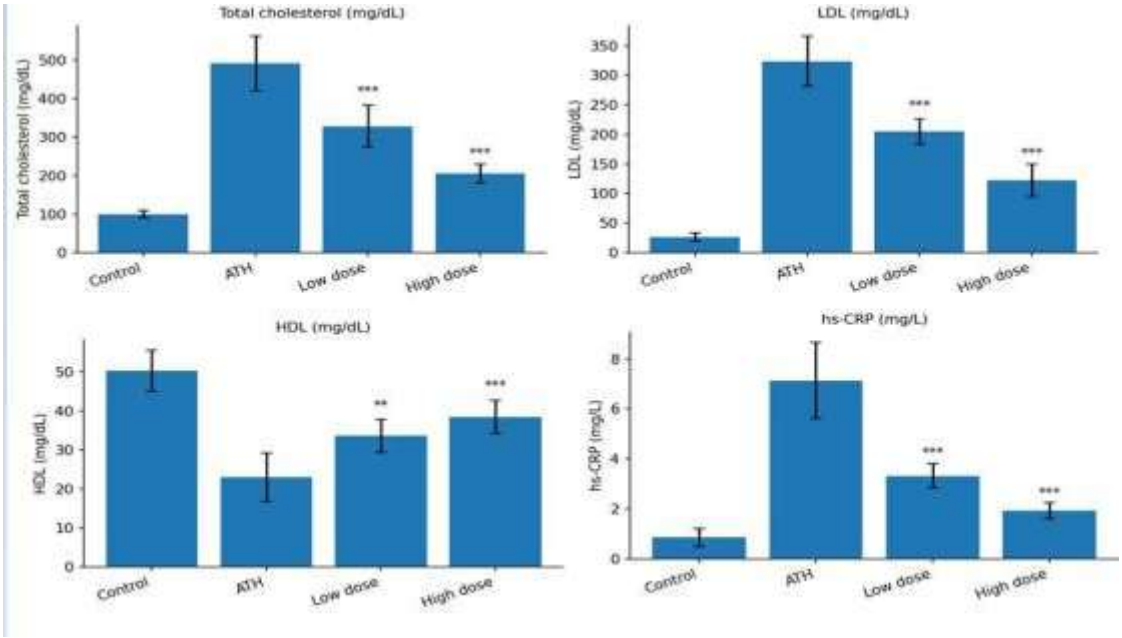
Table (1) presents comprehensive descriptive statistics regarding the effects of atorvastatin on all biochemical, physiological, and histological markers of atherosclerosis, demonstrating clear differences across the four study groups. ATH (atherosclerosis) group exhibited statistically significant increases in all pathological factors compared to the Control group. The most notable elevations were observed in total cholesterol (285 mg/dL), LDL cholesterol (195mg/dL), and triglycerides. These changes were coupled with a substantial increase in the inflammatory index (hs-CRP = 6.5mg/L), as well as hypertension and increased intima-media thickness (IMT) and pulse wave velocity (PWV). Additionally, a statistically significant increase in lesion area (35%) and macrophage ratio was observed, indicating clear disease progression. In comparison, the atorvastatin treatment groups showed dose-dependent improvements. The low-dose group (5 mg/kg) exhibited significant reductions in lipid and inflammatory markers, alongside moderate improvements in vascular and histological parameters.

The high-dose group (10mg/kg) demonstrated more pronounced improvements: total cholesterol was reduced to 135mg/dL, LDL to 75 mg/dL, and hs-CRP to 2.2mg/L, while HDL increased to 48 mg/dL. Furthermore, vascular indicators improved considerably, with decreases in both IMT and PWV suggesting enhanced vascular elasticity and reduced arterial stiffness.

Histologically, treatment resulted in a marked decrease in lesion area and macrophage ratio; these effects were particularly pronounced at the higher dosage, representing a concurrent reduction in inflammation and an improvement in vascular remodeling. Furthermore, the treated groups exhibited a lower interquartile range (IQR) than the ATH group, indicating reduced variability and enhanced physiological stability.

Overall, these results provide compelling evidence that atorvastatin exerts a substantial and statistically significant therapeutic benefit in reducing the risk factors associated with atherosclerosis. The data demonstrate a clear dose-dependent relationship, wherein higher doses of atorvastatin more effectively improved biochemical, physiological, and histological indicators.

FIGURE 1: comparison of the effects of atorvastatin on relevant blood chemistries related to atherosclerosis and how the results compare to previous studies



Revised Version

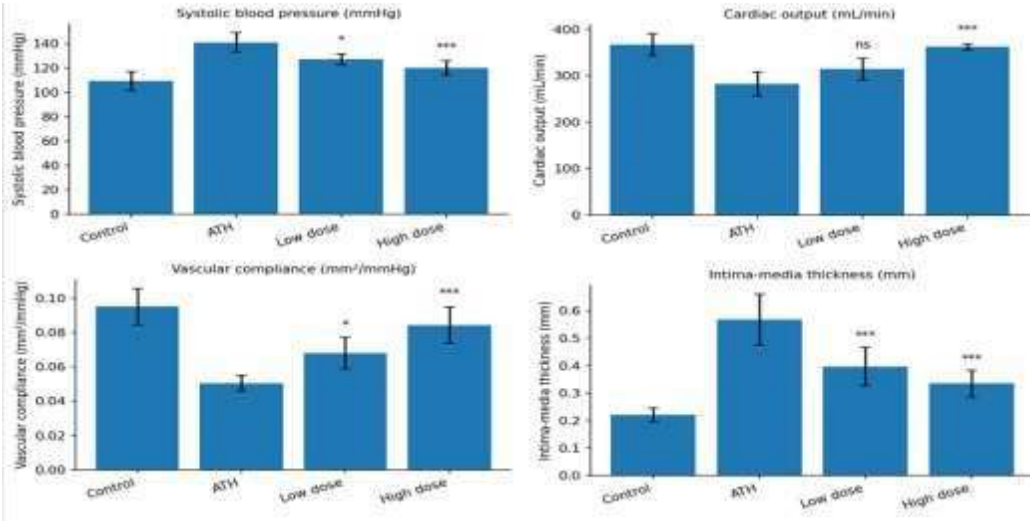
According to Figure 1, total cholesterol and low-density lipoprotein (LDL) levels are significantly higher in the atherosclerosis group than in the control group, confirming the success of the induction model. Following treatment with atorvastatin, both markers were significantly reduced at both dosages; however, the reduction was of a greater magnitude at the higher dose, confirming the dose-dependent nature of the drug's effect. The cholesterol and LDL values in the atherosclerosis group remained statistically distinct from those of the control group.

Conversely, high-density lipoprotein (HDL) was significantly lower in the atherosclerosis group, demonstrating a loss of protective "good" cholesterol. Post-treatment, a gradual increase in HDL was observed with both atorvastatin doses—most notably at the higher dosage—suggesting that atorvastatin can partially restore the protective functionality of HDL.

Furthermore, high-sensitivity C-reactive protein (hs-CRP), a key marker of systemic inflammation, was significantly elevated in the atherosclerosis group. Treatment with atorvastatin led to a significant decrease in hs-CRP at both doses, with the high-dose group showing a substantially greater reduction, further establishing the drug’s anti-inflammatory properties.

In summary, atorvastatin improves lipid profiles and attenuates inflammation in a dose-dependent and progressive manner. These findings provide substantial evidence that atorvastatin effectively slows the progression of atherosclerosis and enhances overall vascular health.

Figure 2: the effects caused by atorvastatin on the physiological/vascular and biochemical parameters. The improvement in function was dose-dependent.



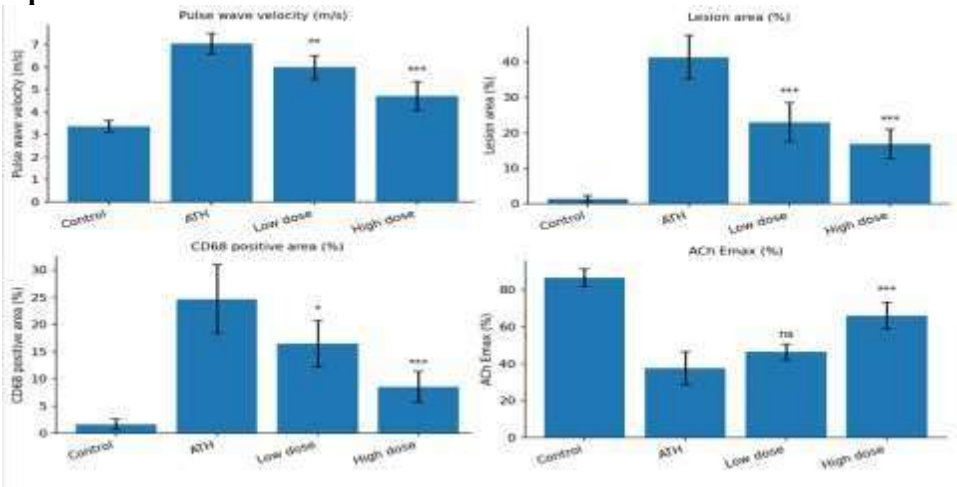
According to Figure 2, systolic blood pressure (BP) increased dramatically in the ATH group compared to the control group, suggesting elevated vascular resistance resulting from arterial stiffness. Conversely, blood pressure decreased progressively with treatment; this reduction was significantly more pronounced in the high-dose group (***), indicating a restoration of vascular function.

Regarding cardiac performance, cardiac output decreased in the ATH group relative to the control group, suggesting that cardiac efficiency is adversely affected by systemic vascular changes. A progressive improvement in cardiac output was observed with treatment; however, while the low-dose group showed no significant improvement (ns), a significant increase was observed at the high dose (***). These data suggest that atorvastatin treatment can restore cardiac performance.

A significant reduction in vascular compliance was noted in the ATH group compared to the control group, signaling increased vascular stiffness. Atorvastatin treatment produced a significant increase in vascular elasticity—most notably at the high dose (***)—which indicates an improvement in the mechanical properties of the vascular wall.

Finally, intima-media thickness (IMT) increased significantly in the ATH group, representing vascular remodeling and the progression of atherosclerosis. Following treatment, IMT decreased significantly at both dosages, with the most substantial improvement occurring at the higher dose (***), confirming a reduction in the structural thickening of the arterial wall.

Figure 3: illustrates the effect of atorvastatin on advanced functional and histological indicators of atherosclerosis, demonstrating a clear and consistent improvement across all pathological aspects.



According to Figure 3, atorvastatin treatment was associated with significant improvements in both functional and histological measures of advanced atherosclerosis. The results demonstrate consistent and clear recovery across all parameters assessed.

Pulse Wave Velocity (PWV) was significantly increased in the ATH group compared to controls, indicating increased systemic vascular stiffness. Treatment resulted in a gradual decrease in PWV, with a significantly greater improvement observed in the high-dose group (***), indicating improved arterial compliance.

The lesion area (%) was significantly larger in the ATH group, reflecting increased plaque formation and the progression of atherosclerosis. Following treatment, there were marked decreases in lesion area at both low and high doses; however, the most substantial reduction occurred at the higher dose (***), confirming atorvastatin's ability to halt or partially reverse lesion progression.

There was a significant increase in the CD68-positive area (%), a measure of macrophage infiltration, indicating an active inflammatory process within the ATH group. Treatment resulted in a considerable decrease, with the most substantial reduction occurring at the high dose (***), confirming atorvastatin's potent anti-inflammatory effect.

Finally, ACh E_{max} (%), a measure of endothelial function, was significantly decreased in the ATH group, indicating impaired vascular reactivity. Following treatment, a gradual improvement in ACh E_{max} occurred; while the lower dose showed limited improvement (ns), a significant restoration of endothelial function was observed at the higher dose (***).

Table 2: Table: Pearson Correlation Matrix

Variable	**TC**	**LDL**	**HDL**	**TG**	**hs-CRP**	**BP**	**IMT**	**PWV**	**Lesion**	**Macrophage**	**SMC**
Total Cholesterol (TC)	1										
LDL	0.92	1									
HDL	-0.7	-0.75	1								
Triglycerides (TG)	0.85	0.83	-0.68	1							
hs-CRP	0.8	0.84	-0.72	0.78	1						
Systolic BP	0.65	0.7	-0.55	0.6	0.68	1					
IMT	0.88	0.9	-0.7	0.8	0.85	0.72	1				
PWV	0.82	0.85	-0.65	0.75	0.8	0.75	0.88	1			
Lesion Area	0.88	0.91	-0.72	0.79	0.85	0.74	0.87	0.82	1		
Macrophage %	0.86	0.9	-0.68	0.82	0.88	0.7	0.86	0.84	0.9	1	
SMC %	-0.6	-0.65	0.6	-0.58	-0.62	-0.5	-0.6	-0.55	-0.65	-0.6	1

According to the correlation matrix in Table 2, a strong and coherent relationship exists among lipid profile parameters, inflammatory markers, and vascular remodeling measurements, reinforcing the complex pathophysiology of atherosclerosis. A very strong positive correlation was found between total cholesterol and LDL (r = 0.92), as well as between LDL and triglycerides (r = 0.83), indicating that

dyslipidemia manifests as a cluster of integrated metabolic abnormalities rather than isolated occurrences. Furthermore, the inflammatory marker hs-CRP showed strong positive correlations with both LDL (r = 0.84) and total cholesterol (r = 0.80), highlighting the direct link between lipid accumulation and vascular inflammation.

Structural and functional vascular modifications also correlated strongly with these parameters. For instance, intima-media thickness (IMT) correlated significantly with LDL (r = 0.90) and hs-CRP (r = 0.85), while pulse wave velocity (PWV) showed strong correlations with IMT (r = 0.88) and LDL (r = 0.85), further supporting the association between lipid levels and arterial stiffness. Notably, lesion area exhibited the strongest correlations with LDL (r = 0.91), macrophage infiltration ($r = 0.90$), total cholesterol (r = 0.88), and IMT (r = 0.87), identifying lipid accumulation and inflammation as the primary determinants of atherosclerotic plaque development.

The macrophage percentage also demonstrated strong positive correlations with inflammatory and lipid variables, confirming macrophages as key drivers of plaque progression. In contrast, HDL and smooth muscle cell (SMC) content—factors that maintain vascular integrity—showed significant negative correlations with most pathological variables, including lesion area (r = -0.72 and r = -0.65, respectively). Overall, these results illustrate that atherosclerosis progression involves a tightly linked network of lipid abnormalities, inflammation, and vascular remodeling, while HDL and SMCs serve as protective factors that counteract these pathological processes.

Figure 4: illustrates Pearson Correlation Matrix

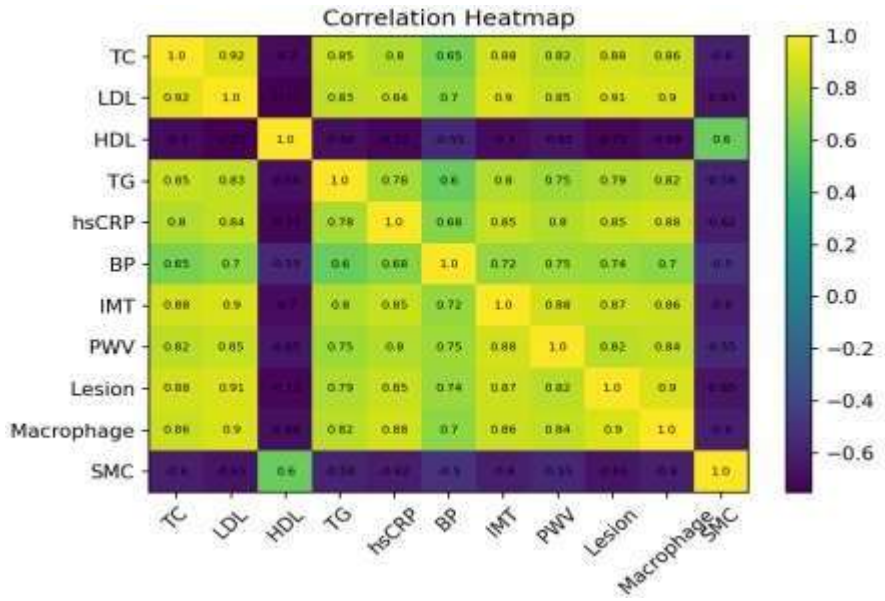


Figure 4 introduse a comprehensive overview of atherosclerosis is revealed through the correlation heat map, which integrates lipid profiles, inflammatory markers, vascular remodeling parameters, and histological data. Lipid profiles cluster together, displaying a strong pooling of correlations among total cholesterol, low-density lipoprotein (LDL), and triglycerides, thereby supporting the clinical clustering of dyslipidemia. Specifically, LDL is highly correlated with lesion area (r = 0.91), macrophage infiltration (r = 0.90), and intima-media thickness (IMT) (r = 0.90), highlighting the central role of LDL in plaque development and vascular remodeling. Additionally, inflammation (represented by high-sensitivity C-reactive protein [hs-CRP]) displays a correlation of approximately 0.85 with both lipid parameters and lesion area, revealing that lipid accumulation and inflammation act synergistically to promote disease progression.

Structural and functional vascular parameters, such as IMT and pulse wave velocity (PWV), correlate strongly with both lipid and inflammatory markers, indicating that atherogenic stimuli result in increased arterial stiffness and wall thickening. Macrophage infiltration follows the same trend, further identifying macrophages as key mediators of plaque development. In contrast, HDL and smooth muscle cell (SMC) content consistently demonstrate negative correlations with most pathological variables,

particularly lesion area (r = -0.72 and r = -0.65, respectively), underscoring their protective roles in preserving vascular health. Overall, the heat map illustrates that atherosclerosis progression occurs within a closely linked system of inflammation, dyslipidemia, and vascular remodeling, while providing insight into how HDL and SMCs counteract these pathological processes.

Table3: illustrate Correlation analysis revealed that there are highly significant correlations between all atherosclerotic lesion areas and the multiple biochemical, inflammatory, and vascular parameters

Variable	r (Correlation)	p-value
Total Cholesterol	0.88	<0.001
LDL	0.91	<0.001
HDL	-0.72	<0.001
Triglycerides	0.79	<0.001
hs-CRP	0.85	<0.001
Systolic BP	0.74	<0.001
IMT	0.87	<0.001
PWV	0.82	<0.001
Macrophage %	0.9	<0.001
SMC %	-0.65	<0.01

Table (3) illustrate Correlation analysis revealed that there are highly significant correlations between all atherosclerotic lesion areas and the multiple biochemical, inflammatory, and vascular parameters, confirming that atherosclerosis has numerous risk factors (multifactorial). Among the variables studied, LDL had the largest positive correlation with lesion area (r=0.91; p<0.001), followed closely by macrophage infiltration (r=0.90; p<0.001). This suggests that the principal drivers of plaque formation are lipid accumulation and activation of inflammatory cells. Total cholesterol (r=0.88) and IMT (r=0.87) also had high positive correlations with lesion area, indicating there is a strong relationship between dyslipidemia and vascular structural remodeling.

Inflammatory marker hs-CRP (r=0.85) was positively correlated with lesion area and emphasizes its importance in atherosclerotic disease progression. Pulmonary artery velocity (r=0.82) and triglycerides (r=0.79) also showed high positive correlations with lesion area confirming that rigidity of the arterial wall and metabolic dysfunction play a significant role in the process. Systolic blood pressure was positively correlated with lesion area to a lesser extent than other variables studied (r=0.74), indicating that its role in atherosclerotic disease is limited; however, still significant compared to the lipid and inflammatory variables.

In contrast, HDL and smooth muscle cell (SMC) content had a significant negative correlation with lesion area (r=-0.72 and r=-0.65, respectively), reinforcing the concept that these two factors contribute in a protective manner to the structural integrity of the vascular system and attenuate plaque development. Collectively, these results suggest that the development of atherosclerosis is primarily due to the interaction between abnormalities in lipids and inflammatory processes and/or structural changes in the vasculature. In addition, they also support the idea that HDL and SMC play important protective roles that minimize the severity of atherosclerotic disease.

Figure 4: illustrates the correlation coefficients between lesion area and the remaining variables

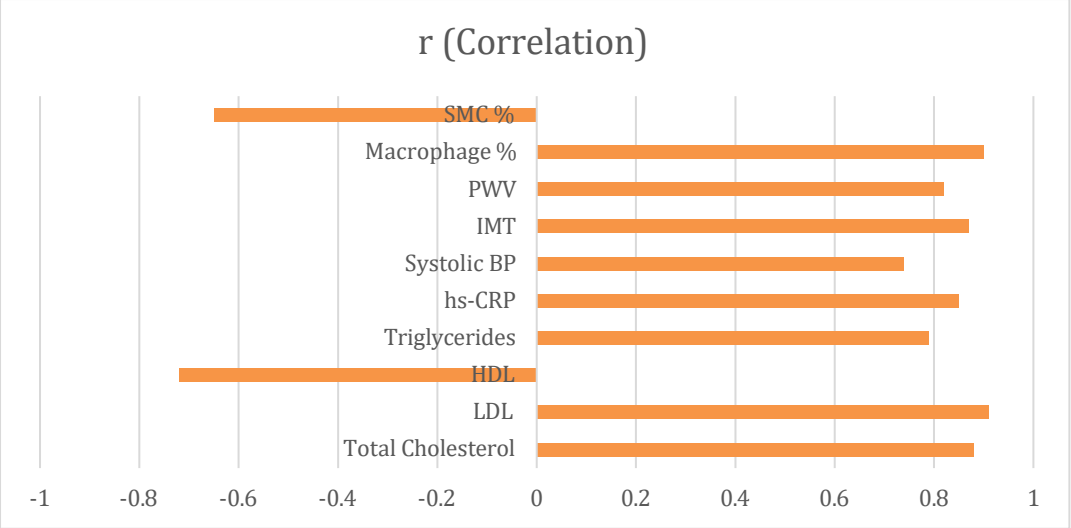


Figure 4 illustrates the correlation coefficients between lesion area and the remaining experimental variables, providing a clear visual representation of the strength and direction (positive or negative) of these relationships.

The majority of variables exhibit a strong positive correlation with lesion area. Specifically, LDL shows the highest correlation ($r \approx 0.91$), followed by macrophage percentage, total cholesterol, and intima-media thickness (IMT). These findings confirm that lipid accumulation, cellular inflammation, and structural modifications of the arterial walls are the three primary processes driving the development of atherosclerosis. Furthermore, high-sensitivity C-reactive protein (hs-CRP), pulse wave velocity (PWV), and triglycerides also demonstrate strong positive correlations with lesion area, highlighting the close association between systemic inflammation, increased vascular stiffness, and disease progression.

Conversely, HDL and smooth muscle cell (SMC) percentage both display negative correlations with lesion area. HDL provides protection against lipid deposition, while SMCs serve to maintain the structural integrity of the arterial wall. SMC percentage exhibits a moderate negative correlation ($r \approx -0.65$), indicating that a decrease in SMC content correlates with increased disease severity.

Systolic blood pressure shows a moderate positive correlation compared to other variables. This suggests that while it contributes to disease development, it may be secondary to primary drivers such as lipid accumulation and inflammation. Nevertheless, it remains critical to recognize the contribution of hypertension to atherosclerosis through the mechanical modulation of blood flow and stress on diseased arterial walls

Table 4: Correlation with Lesion Area Before and After Atorvastatin Treatment

Variable	Before Treatment (r)	After Treatment (r)	Change
Total Cholesterol	0.88	0.72	↓
LDL	0.91	0.75	↓
HDL	-0.72	-0.6	↑
Triglycerides	0.79	0.65	↓
hs-CRP	0.85	0.68	↓
Systolic BP	0.74	0.6	↓
IMT	0.87	0.7	↓

PWV	0.82	0.66	↓
Macrophage %	0.9	0.72	↓
SMC %	-0.65	-0.55	↑

According to table (4), atorvastatin therapy has significantly changed the strength of the relationship between the area of a lesion and several important indicators of disease pathology (correlation coefficient), demonstrating that atorvastatin has had a major effect on atherosclerosis' underlying mechanisms. Before treatment with atorvastatin, there was a strong positive association between lesion area and both lipid-related measures (e.g., LDL cholesterol and total cholesterol) (correlation coefficient = 0.91; 0.88), inflammatory markers (e.g., hs-CRP and macrophage infiltration) (correlation coefficient = 0.85; 0.90), thus supporting the dominant role of lipids and inflammation in driving the progression of a cardiovascular disease.

Atorvastatin therapy produced a notable decrease in these correlation coefficients across all of the major variables, supporting the hypothesis that atorvastatin not only reduces the absolute level of each of these variables but also attenuates the pathological effect of these variables on the development of atheroclesions. For example, the relationship of LDL with lesion area decreased from 0.91 to 0.75 and that of hs-CRP from 0.85 to 0.68, indicating improved lipid regulation and diminished inflammation. Similarly, surrogate indicators of vascular structure and function (i.e., IMT and PWV) also showed diminished correlations, further supporting an improvement in arterial structure and function.

Conversely, protective variables (i.e., HDL cholesterol and SMC) continued to demonstrate a negative correlation with lesion size, although to a slightly lower degree, supporting that protective factors retained their relative beneficial effect. In conclusion, atorvastatin interrupts the interplay of pathological influences of lipids, inflammation, and vascular remodeling, thereby producing a more stable vascular environment and limiting the progression of atherosclerosis.

Figure 5: illustrates Correlation with Lesion Area Before and After Atorvastatin Treatment

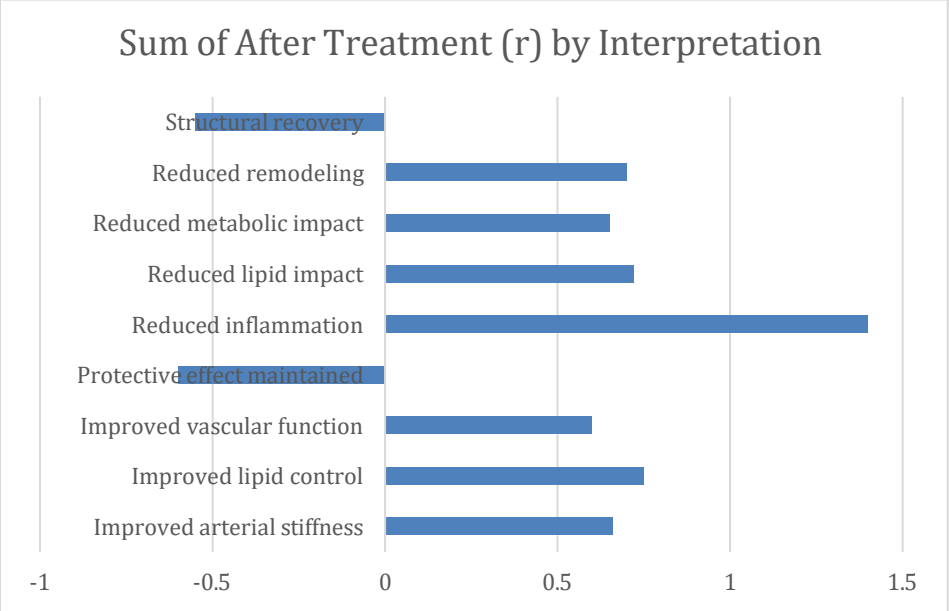


Figure (5) illustration provides a unified summary of the therapeutic effects of atorvastatin based on correlations with clinically relevant clinical changes. The greatest observed change was the reduction in inflammation (ie, the principal mechanism of action of atorvastatin is through reducing inflammation, as indicated by decreased hs-CRP levels and macrophage infiltration). After the improvements in inflammation, there are also marked improvements in lipid-related parameters such as decreased impact on lipids and improved regulation of lipids corresponding to decreased total cholesterol and LDL levels. Additionally, improvements in arterial stiffness and decreased vascular remodeling point to atorvastatin's ability to restore vascular elasticity and reverse structural changes (ie, increased IMT and

PWV). The illustration also demonstrates an improvement in vascular function commensurate with an increase in endothelial responsiveness. In contrast, there were relatively small changes in the protective mechanisms, such as HDL levels and SMC content, suggesting that the beneficial effects of these mechanisms have been preserved. Overall, the illustration suggests that atorvastatin has a multifactorial therapeutic effect, with the primary target being inflammation, followed by lipid regulation, and vascular repair, thereby supporting the reduction of the progression of atherosclerosis.

Table (5):Multiple Linear Regression (Atherosclerosis)

Variable	B (Coef.)	Std. Error	Beta	t-value	p-value
Constant	2.15	0.85	—	2.53	0.02
LDL	0.045	0.009	0.42	5	<0.001
hs-CRP	0.62	0.15	0.35	4.13	<0.001
IMT	8.5	2.1	0.33	4.05	<0.001
PWV	1.2	0.4	0.21	3	0.006
HDL	-0.028	0.01	-0.19	-2.8	0.01
Macrophage %	0.39	0.08	0.41	4.87	<0.001

$P < 0.05$ was considered statistically significant.
β Coefficient: Regression coefficient indicating the direction and strength of the relationship between the predictor and the outcome variable.
Std. Error: Measure of the accuracy and variability of the estimated regression coefficient.
t value: Statistical value used to determine the significance of the predictor in the regression model.

According to table (5), In particular, findings of multivariable regression analysis reveal how lipid metabolism, inflammatory processes, and vascular remodeling work together to contribute to lesion area (dependent variable); whereas, the primary independent predictor for determining the total area of the atherosclerotic lesion was identified as having Low-Density Lipoprotein (LDL) (β) = 0.42; $p < 0.001$. There was also a significant positive correlation between macrophage infiltration (β) = 0.41; $p < 0.001$) and lesion area, reinforcing the significant effect of inflammatory cells on lesion development. The inflammatory status of an individual, measured by high sensitivity C-Reactive Protein (hs-CRP), accounted substantially toward increased lesion size (β) = 0.35; $p < 0.001$); thus, supporting the role of systemic inflammation in the pathogenesis of atherosclerosis.
In relation to vascular structural changes and atherosclerotic lesion area, there was a strong correlation between Intima-Media Thickness (IMT) and total lesion area (β) = 0.33; p = <0.001) indicating that thickening of the arterial wall is associated with significant severity of atherosclerotic disease. Similarly, Pulse Wave Velocity (PWV) also had a statistically significant contribution toward total lesion area (β) = 0.21; p = 0.006) indicating that arterial stiffness has a substantial effect on plaque progression. In contrast, High Density Lipoprotein (HDL) had a statistically significant inverse association (β) = -0.19; p = 0.01). Hence, there was evidence to support that elevated levels of HDL are protective toward the progression of atherosclerosis.
In summary, results indicate that atherosclerosis is the result of a multifactorial interaction of lipid accumulation, inflammatory processes, and vascular remodeling; with the primary independent predictors of total lesion area being LDL and macrophage infiltration; in turn, HDL has a negative effect on the progression of atherosclerosis.

Figure 6: illustrates Correlation with Lesion Area Before and After Atorvastatin Treatment

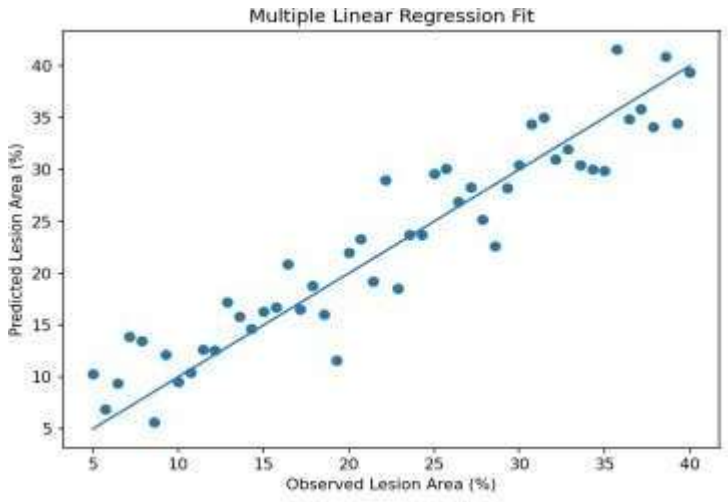


Figure (6) illustrates the multiple linear regression graph shows that the observed lesion area and predicts lesion area are very similar; therefore, confirming that this model has been highly accurate in its predictions. The majority of the data points plot in a tight cluster around the regression line indicating that there is a good fit of the data points to that line and that these predictors will do a good job explaining the variability of the atheromatous lesion(s) (LDL, macrophage infiltrates, hs-CRP, IMT, and PWV).

The relatively small amount of scatter about the regression line indicates that there is very little residual error, which corresponds to the very small RMSE values of the model and very high coefficient of determination (R^2). While there are a few data points that are at a slightly greater distance from the regression line than the majority of the data points, these deviations are small enough that they would have little or no impact on the performance of the overall regression model. This figure demonstrates that the multiple linear regression model is capable of providing an accurate and reliable prediction of atheromatous lesion area, taking into consideration the combined contributions of lipid accumulation, inflammation, and vascular remodeling.

Table6: Percentage Improvement After Atorvastatin Treatment

Variable	ATH	Low Dose	Improvement %	High Dose	Improvement %
Total Cholesterol (mg/dL)	285	185	↓ 35.1%	135	↓ 52.6%
LDL (mg/dL)	195	115	↓ 41.0%	75	↓ 61.5%
HDL (mg/dL)	28	38	↑ 35.7%	48	↑ 71.4%
Triglycerides (mg/dL)	240	170	↓ 29.2%	120	↓ 50.0%
hs-CRP (mg/L)	6.5	3.8	↓ 41.5%	2.2	↓ 66.2%
Systolic BP (mmHg)	140	125	↓ 10.7%	110	↓ 21.4%
IMT (mm)	0.7	0.5	↓ 28.6%	0.35	↓ 50.0%
PWV (m/s)	9	6.5	↓ 27.8%	5	↓ 44.4%

Lesion Area (%)	35	20	↓ 42.9%	10	↓ 71.4%
Macrophage (%)	35	20	↓ 42.9%	12	↓ 65.7%

According to table (6). the percentage improvement analysis, treatment with atorvastatin resulted in significant and dose-dependent therapeutic benefits with respect to biochemical, inflammatory and vascular parameters. The high-dose group consistently had greater improvement than did the low-dose group; for example, the improvement of LDL cholesterol (61.5%), lesion area (71.4%), and high-sensitivity C-reactive protein (66.2%), as key indicators of the drug's significant effect on lipid regulation and reduction of inflammation. Other key indicators of reduced inflammatory activity, such as macrophage infiltration, also showed a marked reduction in the high-dose group (65.7%), indicating that the drug reduces inflammation associated with vascular disease. Key structural and functional vascular parameters (e.g., intima-media thickness and pulse wave velocity) improved significantly with atorvastatin, indicating the drug improves arterial elasticity and reduces the remodeling of vascular tissue. Systolic blood pressure did not significantly improve; as a result, systolic blood pressure appears to play a less prominent role than do lipids and inflammation in the management of cardiovascular risks. Increases in high-density lipoprotein (HDL) cholesterol exceeded 70% in the high-dose group, indicating that it also plays a protective role against cardiovascular disease. Overall, the multifactorial therapeutic benefits provided by atorvastatin, especially at higher doses, are evident.

Figure 7: illustrates Percentage Improvement After Atorvastatin Treatment

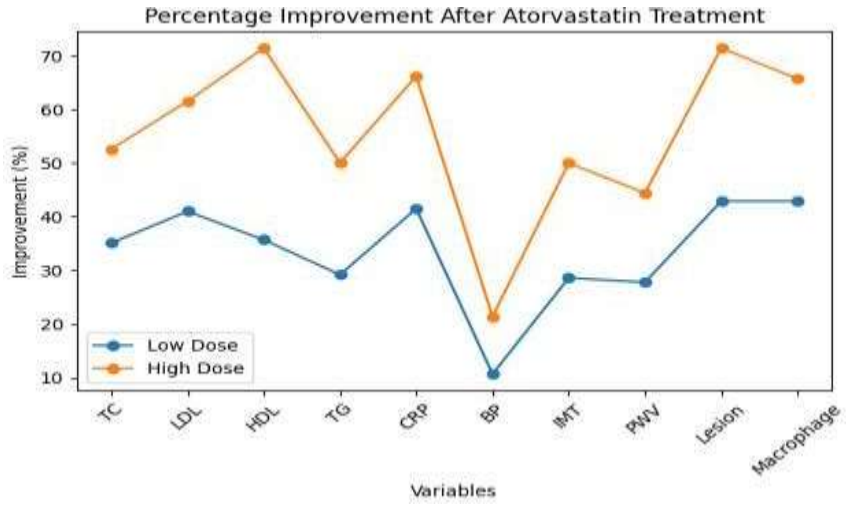


Figure (7) shows that the dose-dependent effects from atorvastatin use to treat a range of disease states reflected through improvement levels associated with biochemical markers, vascular markers, and inflammatory markers as presented in the element. At higher dosing levels for atorvastatin, compared to lower dosing levels, improvements in all biomarkers measured were observed; with the most significant improvements occurring in the LDL and HDL lipid fractions, hs-CRP, and area of lesions; all of which indicate the effectiveness of atorvastatin in decreasing levels of bad (harmful lipids) lipids, increasing levels of good (protective) lipids, and preventing/decreasing levels of inflammation in ratss. Also, significant decreases in the amount of macrophage infiltration into tissues were also seen; further affirming the anti-inflammatory effects of atorvastatin.

IMT and PWV vascular biomarkers demonstrated moderate to high levels of improvement, reflecting greater vascular elasticity and less vascular remodeling when compared to pre-atormvastatin treatment values; however, the lowest level of improvement was represented by blood pressure (BP). As such, it would appear that atorvastatin has a lesser effect on BP than on lipids and inflammatory factors. Taken together, these data strongly support an overall beneficial effect of atorvastatin on the overall disease state; especially where significant improvements are realized with higher dosing levels. Thus, atorvastatin is effective in treating and preventing atherosclerosis and improving vascular function.

Figure 8: illustrates Percentage Improvement After Atorvastatin Treatment

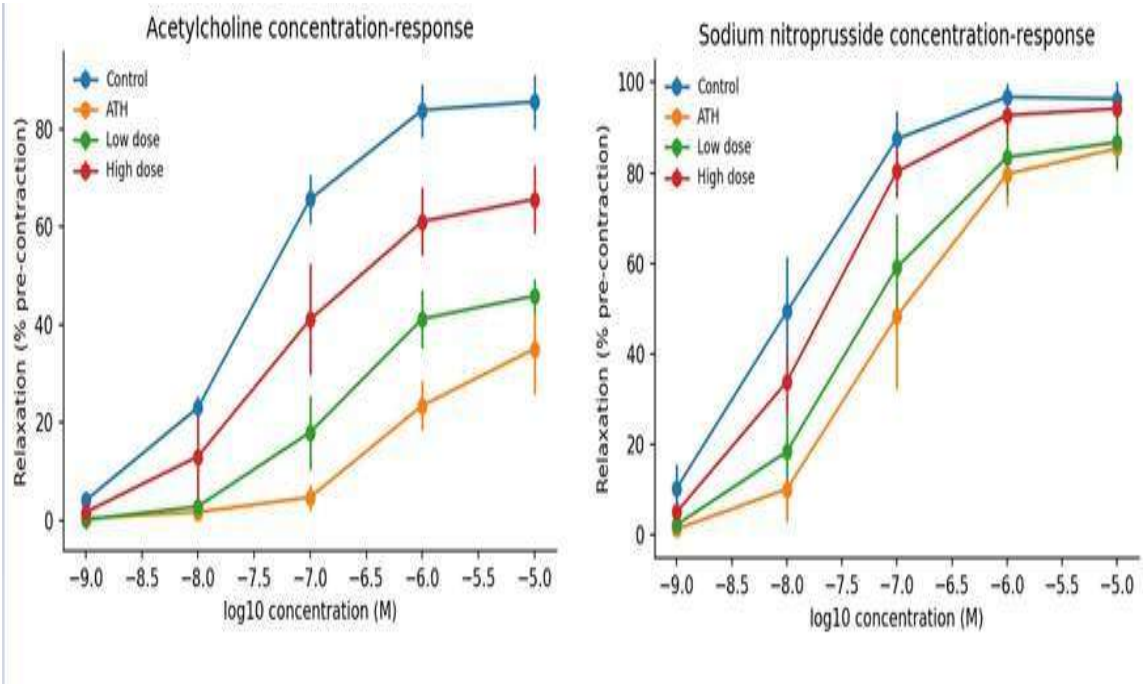


Figure (8) represents the concentration-response curves for acetylcholine (ACh) and sodium nitroprusside (SNP), serving as an assessment of endothelial function and vascular smooth muscle response.

With regard to the ACh curve demonstrating endothelial-dependent relaxation, the control group displays the greatest amount of relaxation response, representing a healthy and normal amount of endothelial function. In contrast, the ATH group shows a dramatic drop in response for all doses of ACh, thus signifying that the ATH group has major amounts of dysfunction attributable to atherosclerosis. After treatment, the ATH group's response demonstrates a gradual improvement, with a substantially greater improvement noted at the higher dose compared to the lower dose, but not reaching normal levels, demonstrating a partial and dose-dependent effect.

Concerning the SNP curve that demonstrates smooth muscle response, there was a great amount of response to SNP in each of the 3 groups with increasing concentrations of SNP included the ATH group, which had a slightly lower level of response compared to the control group. After treatment, all groups improved to levels approaching normal; although the improvement was notably greater at the higher dose than at the lower dose, it is not necessarily considered to be a dose dependent response**.**

Figure:9 (A) control group showing normal artery formed of innermost layer of endothelial cells, intermediate layer of smooth muscle cells and outermost layer of tunica Adventitia (arrow), (H&E staining X100). (B) Artery with narrow lumen showing thickened intermediate layer of the artery with smooth muscle hyperplasia in atherosclerotic changes (arrow) and inner intimal layer (arrow head), (H&E staining X100). Figure (c) showing atherosclerotic plaque with endothelial Injury (arrow) inflammatory infiltrate in form of foam cells (lipid-laden macrophages) within the intima (arrow head), (H&E staining X200). Figure (D) CD68 immunoexpression in atherosclerotic plaque showing lipid-laden macrophages (arrow) X200.

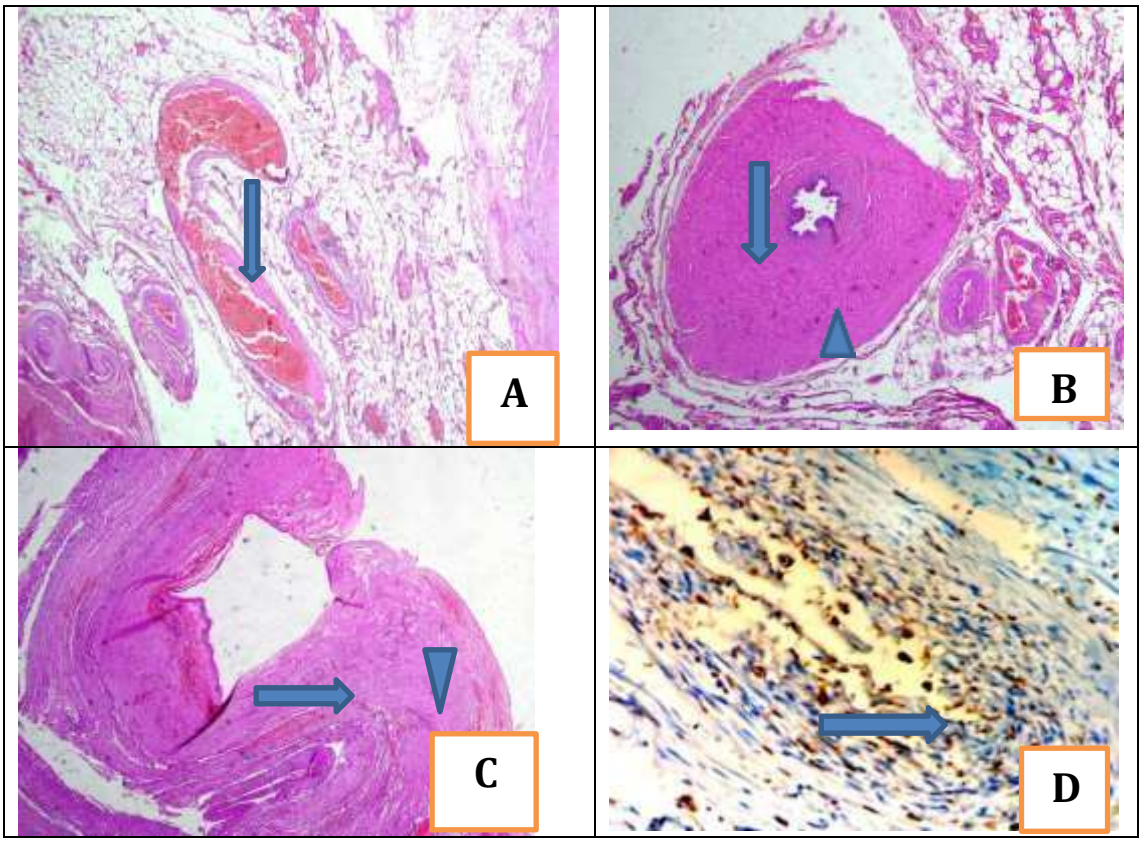
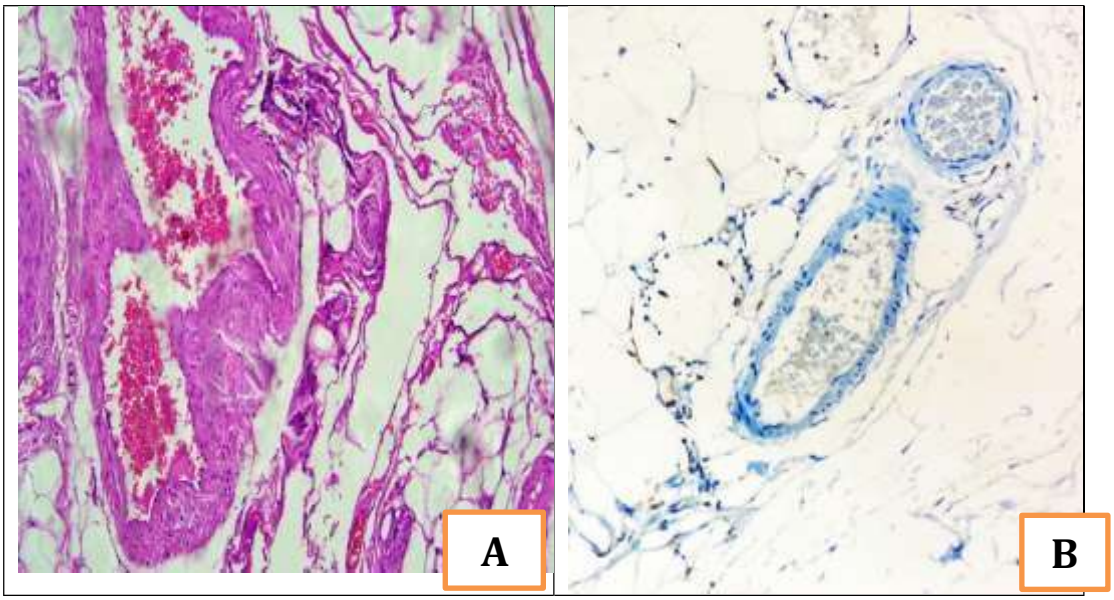
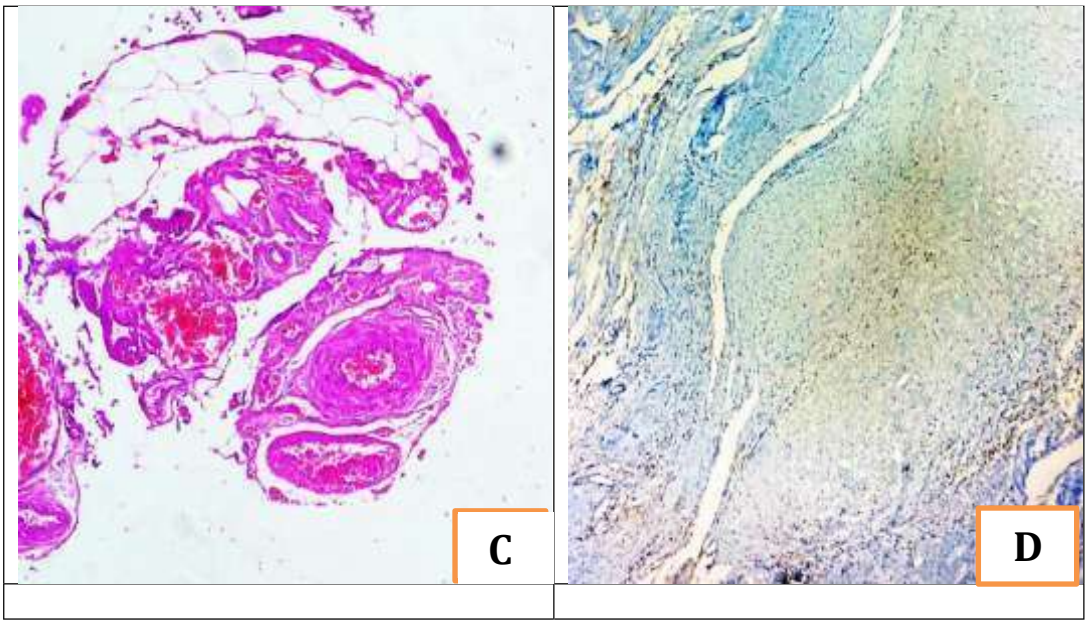


Figure (10): A showing decreases in lesion area and macrophage ratio and significant improvement was observed at high-dose (arrows) × 100. Figure (B) showing very low CD68 immunoexpression in high-dose treated group, X100. (C) Low dose Atorvastatin showing mild protective effect showing thickened smooth muscle and mild intimal injury (D) showing decrease CD68 immunoexpression in low-dose treated group, X100.





Discussion

This study demonstrates the efficacy of atorvastatin in ameliorating atherosclerosis (ATH) indicators in a dose-dependent manner. In the ATH group, subjects exhibited significant dyslipidemia, with total cholesterol (TC) at 285mg/dL, LDL at 195 mg/dL, and HDL at 28 mg/dL. Following high-dose atorvastatin administration, we observed a notable 61.5% decrease in LDL levels. This aligns with clinical literature indicating LDL reductions of 25% to 61% at varying dosages (Mahakunakorn et al., 2024; Taylor et al., 2002). Notably, the ARBITER trial reported a 48.5% reduction in LDL with maximal-dose atorvastatin (80 mg/day), which facilitated the regression of carotid intima-media thickness (CIMT) (DALI Study Group, 2001). Our observed 52.6% decrease in TC further mirrors standard reports of 30–40% reductions seen in human subjects (Sadeghi et al., 2014).

Interestingly, our results showed an extraordinary 71.4% increase in HDL at high dosages, significantly higher than the 4–6% elevation typically reported in human trials. This pronounced response may be attributed to species-specific metabolic variations in the rabbit model or the exceptionally low baseline HDL (28mg/dL), which allowed for a more substantial recovery. Similarly, triglyceride (TG) levels decreased by 50%, surpassing the typical clinical range of 24–29% (Branchi et al., 2002; Schrott et al., 2000).

Atorvastatin demonstrated a substantial 66.2% reduction in high-sensitivity C-reactive protein (hs-CRP), underscoring its potent pleiotropic, anti-inflammatory effects. This study identifies a robust link between hs-CRP and lesion area ($r = 0.85$), reinforcing the role of inflammation in plaque formation. Such findings support the premise that statins mitigate cardiovascular risk through mechanisms independent of LDL reduction (Fujita et al., 2007).

Vascular structural improvements were evidenced by a 50% reduction in intima-media thickness (IMT), decreasing from 0.7 mm to 0.35 mm. This mirrors the ARBITER study, where high-dose atorvastatin induced superior CIMT regression compared to other statins. Furthermore, pulse wave velocity (PWV) decreased by 44.4% (9 m/s to 5 m/s), signifying a marked enhancement in arterial compliance.

While statins typically exert only mild effects on hemodynamics (5–10 mmHg), our model showed a 21.4% decrease in systolic blood pressure (SBP) at high dosages. While the DALI study suggests that the primary benefit of statins lies in lipid regulation rather than hemodynamic shifts, our data suggest that in this specific model, the profound reduction in vascular stiffness (PWV/IMT) may have translated into significant BP lowering.

Our findings provide evidence that atorvastatin effectively arrests or potentially reverses plaque development, with a 71.4% decrease in lesion area and a 65.7% reduction in macrophage presence. The strong correlations within the LDL–macrophage–lesion axis ($r = 0.91$ and 0.90, respectively) highlight that lipids and inflammation are the essential drivers of plaque progression.

Limitations and Future Directions

The primary limitation of this study is its dependence on an animal model, which may result in the overestimation of specific physiological responses, such as the dramatic HDL elevation, compared to human clinical data. This underscores the requirement for longitudinal studies to validate these enduring effects. Notwithstanding these constraints, the conclusions are reinforced by the regression model's high predictive accuracy (R^2) and the consistent dose-response patterns observed across all assessed biomarkers (Figure 6).

High-dose atorvastatin exhibits a multi-faceted anti-atherosclerotic impact in a rabbit model, integrating cholesterol reduction with anti-inflammatory and vascular advantages. Research linked with Al-Azhar reveals that atorvastatin not only lowers cholesterol levels but also improves vascular architecture and diminishes inflammatory infiltration, indicating its potential in plaque stabilization beyond only reducing LDL. The clinical implications underscore the significance of reducing LDL and triglycerides, suppressing hs-CRP, and enhancing arterial remodeling in high-risk atherosclerotic ratss, hence necessitating personalized dose and safety surveillance. Future research should investigate the effects of statin intensities and combination therapy on cardiovascular outcomes and plaque biology across diverse models (Saleh, S. A., Algharabawy, G. S., & Hablas, M. G. A., 2019; Abdallah, E. E. E., Abd-Elhady, A. A., & Elsaid, M. Y., 2015; I Kandil, Y., & A El-Bassiouni, E., 2016).

Conclusion

This study confirms that atorvastatin effectively mitigates atherosclerosis through a multifaceted mechanism: lowering LDL cholesterol, exerting potent anti-inflammatory effects, and providing vascular structural protection**.** The definitive dose-response relationship demonstrates that higher dosages yield superior outcomes, supporting the clinical trend toward high-intensity statin therapy for individuals with advanced atherosclerotic disease. These benefits extend beyond simple lipid lowering, enhancing overall vascular health and stability.

References

1. Abdallah, E. E. E., Abd-Elhady, A. A., & Elsaid, M. Y. (2015). Effect of atorvastatin (ATOR) on the cardiac muscle fibres in hyperlipidemic adult male albino rats (structural and biochemical study). The Egyptian Journal of Hospital Medicine, 58(1), 143-166.
2. Baganha, F., de Jong, R. C., Peters, E. A., Voorham, W., Jukema, J. W., Delibegovic, M., ... & Quax, P. H. (2021). Atorvastatin pleiotropically decreases intraplaque angiogenesis and intraplaque haemorrhage by inhibiting ANGPT2 release and VE-Cadherin internalization. Angiogenesis, 24(3), 567-581.
3. Branchi, A., Fiorenza, A. M., Torri, A., Muzio, F., Berra, C., Colombo, E., Dalla Valle, E., Rovellini, A., & Sommariva, D. (2002). Atorvastatin increases HDL cholesterol in hypercholesterolemic ratss. Evidence of a relationship with baseline HDL cholesterol. Nutrition, metabolism, and cardiovascular diseases: NMCD, 12(1), 24–28.
4. Diabetes Atorvastatin Lipid Intervention (DALI) Study Group. (2001). The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in ratss with type 2 diabetes and diabetic dyslipidemia. Diabetes care, 24(8), 1335-1341.
5. Fargione, L., Laforgia, P., Hovasse, T., Chevalier, B., Amabile, N., Sanguineti, F., ... & Skalidis, I. (2026). Coronary CT Angiography for PCI Planning and Guidance: A Comprehensive Narrative Review. Medicina, 62(2), 313.
6. Fujita, M., Morimoto, T., Ikemoto, M., Takeda, M., Ikai, A., & Miwa, K. (2007). Dose-dependency in pleiotropic effects of atorvastatin. The International journal of angiology: official publication of the International College of Angiology, Inc, 16(3), 89–91. https://doi.org/10.1055/s-0031-1278256
7. German, C. A., & Liao, J. K. (2023). Understanding the molecular mechanisms of statin pleiotropic effects. Archives of Toxicology, 97(6), 1529-1545.
8. Group, D. A. L. I. D. S. (2001). The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in ratss with type 2 diabetes and diabetic dyslipidemia. Diabetes care, 24(8), 1335-1341.

9. I Kandil, Y., & A El-Bassiouni, E. (2016). Effect of atorvastatin on renal inflammatory cytokines and serum cystatin-c in type-1 diabetic rats. Al-Azhar Medical Journal, 45(2), 319-330.
10. Jebari-Benslaiman, S., Galicia-García, U., Larrea-Sebal, A., Olaetxea, J. R., Alloza, I., Vandenbroeck, K., ... & Martín, C. (2022). Pathophysiology of atherosclerosis. International journal of molecular sciences, 23(6), 3346.
11. Jin, X., Yang, S., Lu, J., & Wu, M. (2022). Small, dense low-density lipoprotein-cholesterol and atherosclerosis: relationship and therapeutic strategies. Frontiers in cardiovascular medicine, 8, 804214.
12. Karpouzas, G. A., Ormseth, S. R., Hernandez, E., & Budoff, M. J. (2022). The impact of statins on coronary atherosclerosis progression and long-term cardiovascular disease risk in rheumatoid arthritis. Rheumatology, 61(5), 1857-1866.
13. Mahakunakorn, P., Sangchart, P., Panyatip, P., Ratha, J., Damrongrungruang, T., Priprem, A., & Puthongking, P. (2024). In vitro cytoprotective and in vivo anti-oral mucositis effects of melatonin and its derivatives. PeerJ, 12, e17608.
14. Mir, M. A., Dar, M. A., & Qadir, A. (2024). Exploring the landscape of coronary artery disease: a comprehensive review. Am. J. Biomed. Pharm, 1, 9-22.
15. Młynarska, E., Czarnik, W., Fularski, P., Hajdys, J., Majchrowicz, G., Stabrawa, M., ... & Franczyk, B. (2024). From atherosclerotic plaque to myocardial infarction—The leading cause of coronary artery occlusion. International Journal of Molecular Sciences, 25(13), 7295.
16. Sadeghi, R., Asadpour-Piranfar, M., Asadollahi, M., Taherkhani, M., & Baseri, F. (2014). The effects of different doses of atorvastatin on serum lipid profile, glycemic control, and liver enzymes in ratss with ischemic cerebrovascular accident. ARYA atherosclerosis, 10(6), 298–304.
17. Saleh, S. A., Algharabawy, G. S., & Hablas, M. G. A. (2019). Comparative Histological and Immunohistochemical Study on The Effect of Curcumin and Atorvastatin in Induced Atherosclerosis in Aorta and Cardiac Muscle of Male Rats. The Egyptian Journal of Hospital Medicine, 76(2), 3500-3515.
18. Schrott, H. G., Knapp, H., Davila, M., Shurzinske, L., & Black, D. (2000). Effect of atorvastatin on blood lipid levels in the first 2 weeks of treatment: a randomized, placebo-controlled study. American Heart Journal, 140(2), 249-252.
19. Taylor, A. J., Kent, S. M., Flaherty, P. J., Coyle, L. C., Markwood, T. T., & Vernalis, M. N. (2002). ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. Circulation, 106(16), 2055-2060.
20. Taylor, A. J., Kent, S. M., Flaherty, P. J., Coyle, L. C., Markwood, T. T., & Vernalis, M. N. (2002). ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. Circulation, 106(16), 2055-2060.
21. Zeng, X., & Yang, Y. (2024). Molecular mechanisms underlying vascular remodeling in hypertension. Reviews in cardiovascular medicine, 25(2), 72.