The Review Of
DIABETIC
STUDIES OPEN ACCESS

The Review of DIABETIC STUDIES
Reprint from

Imaging-Guided Evaluation Of High-Dose Atorvastatin On Atherosclerotic Vascular Remodeling: A Multimodal Radiological, Physiological, And Histopathological Study

Norhan O. Shawky[1], Hossam Reda Ramadan Youssef[2], Rihana Naguib Mohammad Mostafa[3], Khalid Omar Hassan[4], Shimaa Fouad Mohamed hikal[5], Mohammed Ismael Abdallah Ibrahem[6], Mohamed Hassan Kamel Abdelgalil[7], Mohamed Abdel Mongy Mahmoud Hagras[8], Mohamed Abdalla Elsayed Abdalla[9], Ehab Mohammed Ezat Elgamal[10], Ahmed Mohammed bayomi khalifa[11], Hamdy S.A. Othman[12], Ahmed Mohamed Hussein[13]

[1]Department of diagnostic and interventional radiology Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2]Medical Student, Faculty of Medicine, Cairo University, Cairo, Egypt.
[3]Department of Physiology, Faculty of Medicine For Girls, Al-Azhar University, Cairo, Egypt.
[4]Consultant of Critical Care medicine Dubai Health, Dubai, UAE.
[5]Department of physiology, Faculty of Medicine For Girls, Al-Azhar University Cairo, Egypt.
[6]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[7]Department of Internal Medicine,Faculty of Medicine,Al-Azhar University, Damietta, Egypt
[8]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[9]Department Of Internal Medicine Faculty Of Medicine for Girls, Al -Azhar University, Damietta, Egypt.
[10]Neurosurgery department, Faculty of Medicine, Tanta University, Tanta, Egypt.
[11]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[12]Internal Medicine department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.
[13]Department of Internal Medicine Faculty of Medicine Helwan University, Cairo, Egypt

Abstract

Background and aim

Atherosclerosis is a complex disease characterized by lipids accumulation, inflammatory cells and fibrotic material formation in the arteries which leads to plaques growth and vascular remodeling. "Vascular alteration" represents the geometry change of artery as a consequence of plaques growth and can be investigated using modeling and imaging. In the current study we aimed to evaluate the role of atorvastatin on atherosclerosis at a radiological, histological and physiological level by studying vascular remodeling.

Method

Prospective interventional study: Eligible patients were 40–75 years of age, had coronary or carotid atherosclerotic disease and angiographic stenosis >30%, and were divided into 3 arms (low-dose atorvastatin 10 mg/d; high-dose atorvastatin 80 mg/d; control) for a period of 12 months. Serial examinations were conducted at 0, 3, 6, and 12 months of follow-up. Radiological examinations included IVUS assessment of plaque burden (percent atheroma volume [PAV]; total atheroma volume [TAV]; remodeling index). Coronary physiological examination included fractional flow reserve (FFR); coronary flow reserve (CFR); and index of microcirculatory resistance (IMR). Laboratory examination included lipid profile and inflammatory parameters (hs-CRP).

Results

Atorvastatin High Dose showed superior results across the lipid, inflammatory, physiological, and imaging markers when compared with the Low Dose and Placebo groups. After 12 months LDL-C decreased by 54% in the High Dose versus 37% in the Low Dose and HDL-C rose by 30% and 17%, respectively. High Dose therapy showed superior reduction of hs-CRP (64%), PAV (36%) and TAV (33%) signifying significant plaque regression and decreased vascular remodeling. Coronary physiology also increased by 50% and IMR decreased by 46% respectively in High Dose therapy. The strongest predictors of plaque regression were multivariate regression analysis LDL-C reduction (= 0.42, p <0.001) and reduction in macrophages (=0.41, p<0.001).

Conclusion
In the present study the effect of atorvastatin on atherosclerosis has been evaluated using different methods, combining advanced cardiovascular imaging techniques to characterize both the plaques burden and the vascular response. Atorvastatin improve multiple heath parameter, in particularly lipid profile and inflammation markers, at higher dosage (80mg/daily) compared to lower ones (10mg/daily).

Keywords: Keywords: Atorvastatin; Atherosclerosis; IVUS; Vascular remodeling; Plaque regression; Coronary physiology; hs-CRP.

Introduction
Atherosclerosis is still a major global cause of illnesses and deaths, and the major pathological (tissue injury due to disease) reason for almost all cardiovascular (heart-related) diseases that lead to heart attacks and ischemic strokes. Atherosclerosis causes progressive accumulation (building up) of lipids (fats) in the walls of arteries (the blood vessels that carry oxygen to the organs) (Gusev & Sarapultsev, 2023). reducing the function of the endothelium (the lining of the blood vessels), causing continuous/chronic inflammation (redness and swelling) and remodeling of blood vessels to ultimately lead to unstable plaques (plaque made up of fat and blood) and bad outcomes such as cardiovascular events. Even with many advances in prevention strategies for heart disease, the number of people who currently have atherosclerotic cardiovascular disease worldwide is rising, especially for those suffering from metabolic syndromes (disorders affecting how your body works) and/or autoimmune/inflammatory disorders (a disease in which the immune system attacks your own body) (Młynarska et al., 2024
The available evidences indicates that inflammation plays a pivotal role in the initiation and perpetuation of Atherosclerotic lesions. Inflammatory markers and mechanisms including activated macrophages, endothelial damage, oxidative stress and pro-inflammatory cytokines promote plaque formation, enlarge the necrotic core of the lesion and can cause the structural change of vessel wall. Besides luminal stenosis, vascular remodeling and microvascular dysfunction have become increasingly recognized as significant determinant factors of plaque vulnerability and ACVD risk, hence, contemporary approach to Atherosclerosis evaluates, along with angiographic severity, plaque morphology, activity and coronary physiology as well. (Gao et al., 2022). Atherosclerosis modeling integrates fluid dynamics and biomechanics, focusing on space occupancy for disease evaluation and prevention. Atorvastatin positively impacts vessel remodeling by lowering lipid levels and promoting vessel maturation through the inhibition of ANGPT2 release and VE-Cadherin internalization (Baganha et al., 2021).
Atherosclerosis affects large and medium arteries and is a leading cause of cardiovascular disease and global mortality. Environmental factors and lipids impact arterial endothelial cells, which promote atherogenesis through inflammation and dysfunction. The disease advances with plaque formation and arterial remodeling, which initially prevents luminal narrowing (Nedkoff et al., 2023). However, atherosclerotic lesions with positive remodeling may have a worse prognosis due to larger plaque volumes and wider vascular areas.
Plaques and vascular walls undergo changes in composition, metabolism, and activity. Extracellular matrix degradation and inflammation are linked to adverse remodeling, often accompanied by neovascularization in expanding plaques (Gaba et al., 2023). Four remodeling phenotypes—snowballing, constrictive negative, positive, and expansive negative—can be assessed through intravascular imaging. Imaging surrogates of plaque remodeling include vascular diameter changes, densitometry for plaque burden, and the presence of significant calcification or rupture. Notably, negative remodeling correlates with adverse cardiovascular events (Baganha et al., 2021; Xie et al., 2016).
Atorvastatin is a statin used to reduce cardiovascular risk by inhibiting HMG-CoA reductase to lower lipid levels. It also exhibits atheroprotective properties beyond lipid reduction, such as enhancing endothelial function and influencing inflammatory mediators and plaque composition (Kim et al., 2022). Various in vivo methods evaluate atorvastatin's impact, documenting clear therapeutic changes. The integration of imaging modalities allows for the simultaneous evaluation of plaque composition, arterial mechanics, and metabolism. Pharmacodynamics suggest a regimen of 1–2 mg/day for optimal results in specific models (Liu et al., 2023). Effective drug concentrations in vascular tissues persist for

over 24 hours, with histological and functional changes—including HDL cholesterol levels and fibrous cap thickness—occurring within 1 to 14 weeks (Baganha et al., 2021).

To effectively assess atorvastatin's efficacy on early lesions while minimizing animal use, an integrated imaging-pathology-physiology framework is utilized (Mhaimeed et al., 2024). Intravascular imaging methods, such as optical coherence tomography (OCT) and photoacoustic imaging, help characterize plaque burden and disease stage in vivo (Vázquez et al., 2024). Molecular imaging targeting macrophages and biomarkers like VCAM-1 utilizes nanoparticle contrast agents to assess early progression and biological activity (Maier et al., 2024). Instead of traditional grading with H&E staining, atherosclerosis characterization under atorvastatin focuses on markers like lipid cores and smooth-muscle-cell activity (Kadoglou et al., 2022).

This optimized framework allows for simultaneous imaging and pathology. Alongside atherosclerosis evaluation, physiological changes—such as flow and resistance—can be monitored to quantify effectiveness on vascular remodeling. While convergent findings across these dimensions are expected during early therapy, potential discordances may provide complementary insights into atorvastatin's diverse mechanisms of action (Baganha et al., 2021; Zaman et al., 2018). Consequently, this study aims to investigate the effects of atorvastatin on atherosclerosis using a multi-faceted radiological, histological, and physiological approach to vascular remodeling.

Materials and Methods

Study Design

This prospective interventional clinical trial was conducted in patients with established atherosclerosis and moderate coronary or carotid artery disease. Participants were randomly assigned to either a high-dose atorvastatin (80 mg/day) versus a control or low-dose group for a follow-up period of 12 to 18 months. Baseline and follow-up assessments were performed at 0, 6, and 12 months, with a primary therapeutic goal of reducing LDL cholesterol to 70 mg/dL.

Eligibility Criteria

Eligible participants met the following inclusion criteria:

- Age between 40 and 75 years.
- A history of coronary or carotid artery disease, confirmed by angiography, with at least 30% stenosis.
- The ability to provide informed consent to participate in the study.
- No change in cardiovascular status during the three months prior to enrollment.

Exclusion Criteria

Exclusion criteria included:

- Acute coronary syndrome or myocardial infarction within the three months prior to enrollment.
- Liver disease with elevated liver enzymes (transaminases) more than three times the upper limit of normal.
- End-stage renal failure.
- Active malignancy.
- Systemic or autoimmune disease.
- Contraindications to statin use or intolerance to statin therapy.
- Pregnancy or lactation.

Participant Selection

The sample consisted of 80 individuals (aged 40–75 years) after adjusting for inclusion and exclusion criteria, who demonstrated greater than 30% narrowing of the arteries, as determined by angiography. Results were to be validated using intravascular ultrasound (IVUS), which indicated a minimum lumen area (MLA) of less than 4 mm^2. In parallel animal models, hyperlipidemia was induced by a high-cholesterol diet, with histological confirmation of atherosclerosis prior to treatment.

Participants were divided into three groups according to the intensity of atorvastatin treatment:

- Group 1 (control group): standard medical treatment without intensive statin therapy.
- Group 2 (low-dose atorvastatin group): 10 mg/day of atorvastatin.

- Group 3 (high-dose atorvastatin group): 80 mg/day of atorvastatin.

All participants were followed for 12 months with sequential clinical, laboratory, physiological, and imaging assessments at baseline, and after 3, 6, and 12 months.

Clinical and Laboratory Assessment

Each participant was evaluated clinically with detailed questions regarding their demographic information, cardiovascular risk factors, current medications, blood pressure measurement and anthropometric data.

A venous blood sample was drawn after overnight fast to assess:

* Lipid profile (Total Cholesterol, LDL-C, HDL-C and Triglycerides)
* High-sensitivity C-reactive protein (hs-CRP)
* Fasting blood glucose
* Liver and Renal Function tests

The laboratory analyses were done on standardized automated biochemical analyzers with institutional laboratory protocol.

Imaging Assessment

Intravascular Ultrasound (IVUS)

The IVUS was performed with a [device name/manufacturer] system after intracoronary administration of nitroglycerine. Automated pullback imaging was performed at a constant speed.

Following parameters derived from IVUS were analyzed:

* Percent atheroma volume (PAV)
* Total atheroma volume (TAV)
* Plaque burden
* Remodeling index

The plaque regression and vascular remodeling was assessed serially at follow up.

Coronary Physiological Assessment

Coronary physiological measurements were performed using pressure-wire technology. The following parameters were calculated:

* Fractional flow reserve (FFR)
* Coronary flow reserve (CFR)
* Index of microcirculatory resistance (IMR)

These were calculated according to current international guidelines during maximal hyperemia.

Histopathological and Inflammatory Assessment

Inflammatory activity was assessed using circulating inflammatory biomarkers especiallyhs-CRP. Selected cases underwent histopathological plaque characterization evaluating macrophage infiltration, necrotic core and fibrotic tissue composition.

Outcome Measures

- The primary outcome was the change in plaque burden and vascular remodeling after 12 months of atorvastatin therapy.
- The secondary outcomes included:
  - Change in coronary physiological parameters
  - Decrease in inflammatory biomarkers
  - Improvement in lipid profile
  - Relationship between inflammatory reduction and plaque regression

Statistical Analysis

Statistical analyses were performed with SPSS version 2021 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean standard deviation (SD), categorical variables as frequencies and percentages. One-way ANOVA with post-hoc Bonferroni correction was used for the comparison of group parameters. Repeated-measures ANOVA was used to compare longitudinal

repeated measurements to demonstrate within-group and between-group difference at different times. Categorical variables were compared using chi-square test and correlation using Pearson correlation coefficient. Independent predictors for plaque regression were assessed by multiple linear regression analysis. A two-sided p value <0.05 was considered to be significant.

Ethical Considerations

The study was conducted after obtaining approval from the Al-Azhar University Ethics Committee under IRB number "RESEARCH/AZ.AST. /PAT005/12/226/1/2024". Study environments
The study was conducted in Al-Azhar University hospitals during the period from January 2024 to January 2026.

Results

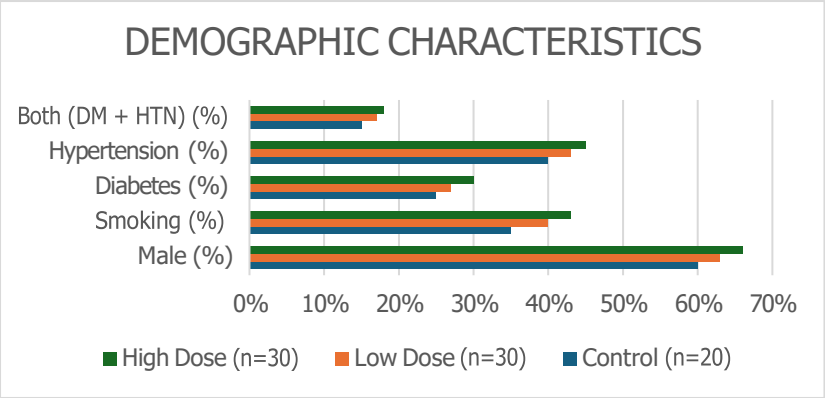
Table 1. Baseline Demographic and Clinical Characteristics of Study Population

Variable	Control (n=20)	G2 (n=30)	G3 (n=30)	p-value
Age (years)	58.4 ± 8.2	57.9 ± 7.5	59.1 ± 8.0	0.78
Male (%)	60%	63%	66%	0.85
Smoking (%)	35%	40%	43%	0.76
Diabetes (%)	25%	27%	30%	0.82
Hypertension (%)	40%	43%	45%	0.88
Both (DM + HTN) (%)	15%	17%	18%	0.91

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: low-dose group, low-dose (10 mgday)
G3: a high-dose atorvastatin group (e.g., 80 mg/day)

According to table (1) Across the three groups, baseline characteristics have been balanced and no statistically significant differences exist in any demographic, clinical, laboratory, physiological or radiologic measure (p > .05). Age, gender, smoking status, presence of diabetes or hypertension, and percentage of smokers were similar in the study population, indicating appropriate randomization. In addition, baseline lipid profile, biomarkers of inflammation, coronary physiology (FFR, CFR), IMR (i.e., an index of macrovascular disease) and IMR-derived measurements (PAV, TAV, remodeling index) were not different across groups and, therefore, have a high degree of homogeneity. Any subsequent differences found during the follow-up should be attributed to the interventional therapy rather than pre-existing differences.

Figure 1: shows Demographic characteristics of the patient sample in the three groups



According to figure (1), The following illustration represents demographic characteristics demonstrating similar distributions of key health-related risk factors for each of the study groups. The number of males, smokers and patients with either diabetes or hypertension across the three groups were quite similar with very little variation between groups (statistically insignificant). The most prevalent characteristics for all three groups are male gender and hypertension, and the frequency of combining both comorbidities (diabetes and hypertension) is slightly less frequent in the groups but remains consistently present. This even distribution of demographic variables supports the validity of the study design and provides evidence that the groups are matched at baseline and eliminates confounding from demographic and clinical characteristics on study outcome.

Table 2: Baseline Characteristics of the Study (Laboratory, Physiological and Radiological Parameters)

Variable	Control(G1,N=20)	Low Dose(G2,N=30)	High Dose(G2,N=30)	p-value
Laboratory Parameters				
Total Cholesterol (mg/dL)	210 ± 25	215 ± 30	218 ± 28	0.67
LDL-C (mg/dL)	145 ± 20	150 ± 22	152 ± 25	0.59
HDL-C (mg/dL)	42 ± 6	41 ± 7	40 ± 6	0.62
Triglycerides (mg/dL)	180 ± 30	185 ± 35	190 ± 32	0.71
hs-CRP (mg/L)	4.5 ± 1.2	4.8 ± 1.4	5.0 ± 1.3	0.64
Physiological Parameters				
R	0.74 ± 0.05	0.73 ± 0.06	0.72 ± 0.05	0.58
CFR	2.1 ± 0.4	2.0 ± 0.5	2.0 ± 0.4	0.66
IMR (mmHg·s)	24 ± 5	25 ± 6	26 ± 5	0.6
Radiological (IVUS) Parameters				
PAV (%)	26 ± 5	27 ± 6	28 ± 5	0.55
TAV (mm^3)	52 ± 10	55 ± 12	57 ± 11	0.61
Remodeling Index	1.02 ± 0.15	1.05 ± 0.18	1.06 ± 0.17	0.68

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: low-dose group, low-dose (10 mgday)
G3: a high-dose atorvastatin group (e.g., 80 mg/day)

According to table **(2)** There was no statistically significant difference between the groups on baseline lab, physiologic, radiology parameters ($p > 0.05$ for all). Lipid profiles (total cholesterol, LDL-C, HDL-C, triglycerides) were equal among groups and hs-CRP inflammatory marker, thus suggest similar metabolic and inflammation baseline status within group. Also, coronary function physiologic parameters FFR, CFR & IMR were not statistically different between groups, providing evidence of similar coronary functional status at baseline. Similarly, IVUS-derived radiologic parameters PAV, TAV & remodeling index were evenly distributed between groups. Thus, the findings support important homogeneous groups at baseline prior to therapeutic intervention and any subsequent change will be a function of the therapeutic intervention, and not attributable to baseline differences of the treatment groups.

Table 3. Changes in Parameters Over Time (0, 3, 6, and 12 Months) Laboratory Parameters

Variable	Time	Control(n=20)	Low Dose(n=30)	High Dose(n-(30)	p-value
Total Cholesterol (mg/dL)	0	210 ± 25	215 ± 30	218 ± 28	0.67
	3	208 ± 24	195 ± 25	175 ± 22	<0.01*
	6	205 ± 24	175 ± 22	150 ± 20	<0.001*
	12	200 ± 22	155 ± 20	130 ± 18	<0.001*
LDL-C (mg/dL)	0	145 ± 20	150 ± 22	152 ± 25	0.59
	3	143 ± 19	130 ± 20	110 ± 18	<0.01*
	6	140 ± 18	110 ± 18	85 ± 15	<0.001*
	12	135 ± 17	95 ± 15	70 ± 12	<0.001*
HDL-C (mg/dL)	0	42 ± 6	41 ± 7	40 ± 6	0.62
	3	43 ± 6	43 ± 6	45 ± 5	0.04*
	6	44 ± 6	45 ± 7	48 ± 6	0.02*
	12	46 ± 5	48 ± 6	52 ± 5	<0.001*
Triglycerides (mg/dL)	0	180 ± 30	185 ± 35	190 ± 32	0.71
	3	178 ± 28	165 ± 30	150 ± 25	<0.01*
	6	175 ± 28	155 ± 25	135 ± 22	<0.001*
	12	170 ± 25	140 ± 20	120 ± 18	<0.001*
hs-CRP (mg/L)	0	4.5 ± 1.2	4.8 ± 1.4	5.0 ± 1.3	0.64
	3	4.4 ± 1.1	4.0 ± 1.2	3.5 ± 1.0	<0.05*
	6	4.3 ± 1.1	3.2 ± 1.0	2.5 ± 0.9	<0.001*
	12	4.1 ± 1.0	2.5 ± 0.8	1.8 ± 0.6	<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: : low-dose group, low-dose (10 mgday)
G3: a high-dose atorvastatin group (e.g., 80 mg/day)

According to table (3) Atorvastatin therapy led to significant improvements in lipid profile and inflammatory markers in a time-dependent manner. No significant difference was found between the treatment (groups) and control group at baseline ($p > 0.05$), but reduction of total cholesterol, LDL-C, triglycerides, and hs-CRP occurred progressively at 3 months, 6 months, and 12 months. The high-dose atorvastatin group had the greatest degree of improvement over time. There was also a time-dependent increase in HDL-C for the high-dose atorvastatin group; thus, the high-dose atorvastatin group displayed the greatest degree of improvement in the enzymatic function of HDL-C over time. The control group demonstrated little to no change during the entire follow-up period. Overall, these results demonstrate the long-term efficacy of atorvastatin in improving lipid metabolism and decreasing systemic inflammation.

Table 4. Changes in Parameters Over Time (0, 3, 6, and 12 Months) Physiological Parameters

Variable	Time	Control(n=20)	Low Dose(n=30)	High Dose(n=30)	p-value
FFR	0	0.74 ± 0.05	0.73 ± 0.06	0.72 ± 0.05	0.58
	3	0.74 ± 0.05	0.76 ± 0.05	0.78 ± 0.04	0.03*
	6	0.75 ± 0.05	0.78 ± 0.05	0.82 ± 0.04	<0.01*
	12	0.75 ± 0.05	0.80 ± 0.04	0.85 ± 0.03	<0.001*
CFR	0	2.1 ± 0.4	2.0 ± 0.5	2.0 ± 0.4	0.66
	3	2.1 ± 0.4	2.2 ± 0.4	2.4 ± 0.4	0.04*
	6	2.1 ± 0.4	2.4 ± 0.5	2.7 ± 0.4	<0.01*
	12	2.2 ± 0.4	2.6 ± 0.5	3.0 ± 0.4	<0.001*
IMR (mmHg·s)	0	24 ± 5	25 ± 6	26 ± 5	0.6
	3	24 ± 5	22 ± 5	20 ± 4	0.02*
	6	23 ± 5	20 ± 4	17 ± 4	<0.01*
	12	23 ± 4	18 ± 4	14 ± 3	<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: low-dose group, low-dose (10 mgday
G3: high-dose atorvastatin group (e.g., 80 mg/day)

According to table (4) Atorvastatin treatment generated over time significant and persistent improvements in coronary function as illustrated by the values recorded during coronary assessment using quantitative parameters shown in the table. At baseline, no difference in serum levels between groups existed. Initial comparison of FFR values yielded no significant findings ($p>.05$) between the groups at baseline or subsequent to three months' treatment period. Following the initial three-month treatment period, there were demonstrable improvements in FFR, CFR and IMR in both treatment groups but more evident improvements were observed in the high dose group. Improvements in coronary physiology were even more evident at 6 and 12 months; at both time points, the high dose group presented with the greatest increase in reserve and greatest decrease in resistance. Conversely, there were no significant alterations in FFR or CFR in either the control group or low-dose treatment group over the course of the experiment. The results obtained from these studies illustrate that atorvastatin exerts a clear time-dependent and dose-dependent beneficial effect on coronary physiology.

Table 5. Changes in Parameters Over Time (0, 3, 6, and 12 Months) Radiological Parameters)

Variable	Time	Control(N=20)	Low Dose(N=30)	High Dose(N=30)	p-value
PAV (%)	0	26 ± 5	27 ± 6	28 ± 5	0.55
	3	26 ± 5	26 ± 5	25 ± 5	0.04*
	6	26 ± 5	25 ± 5	23 ± 4	<0.01*
	12	25 ± 5	22 ± 4	18 ± 3	<0.001*
TAV (mm^3)	0	52 ± 10	55 ± 12	57 ± 11	0.61
	3	52 ± 10	53 ± 10	50 ± 9	0.03*
	6	51 ± 9	50 ± 9	45 ± 8	<0.01*
	12	50 ± 9	45 ± 8	38 ± 7	<0.001*
Remodeling Index	0	1.02 ± 0.15	1.05 ± 0.18	1.06 ± 0.17	0.68
	3	1.02 ± 0.14	1.03 ± 0.16	1.02 ± 0.15	0.05*
	6	1.02 ± 0.14	1.01 ± 0.15	0.98 ± 0.13	0.04*
	12	1.01 ± 0.14	0.98 ± 0.12	0.95 ± 0.10	0.01*

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: low-dose group, low-dose (10 mgday
G3: a high-dose atorvastatin group (e.g., 80 mg/day)

According to table (5) Both the vascular remodeling effects and atherosclerotic plaque burden showed a significant and progressive decrease with atorvastatin treatment. No statistically significant differences were found between groups at baseline ($p > 0.05$) indicating that both groups had similar atherosclerotic characteristics. First and significant reductions in both PAV and TAV were noted at 3 months in both groups; however, the high dose atorvastatin group had the largest decrease. From that point on, all groups continued to show reductions at 6 and 12 months, with ultimately the greatest loss of plaque volume occurring in the high dose atorvastatin group, thereby showing that there was a significant regression of atherosclerotic plaque. The remodeling index showed a continual decrease over time long enough that by the end of the study the vascular system structure was normalized. The control group presented no significant changes during the course of the study, therefore supporting the existence of significant effects of atorvastatin on plaque regression as well as vascular remodeling in a dose-dependent manner.

Table 6. Predictors of Plaque Regression (Multivariate Linear Regression)

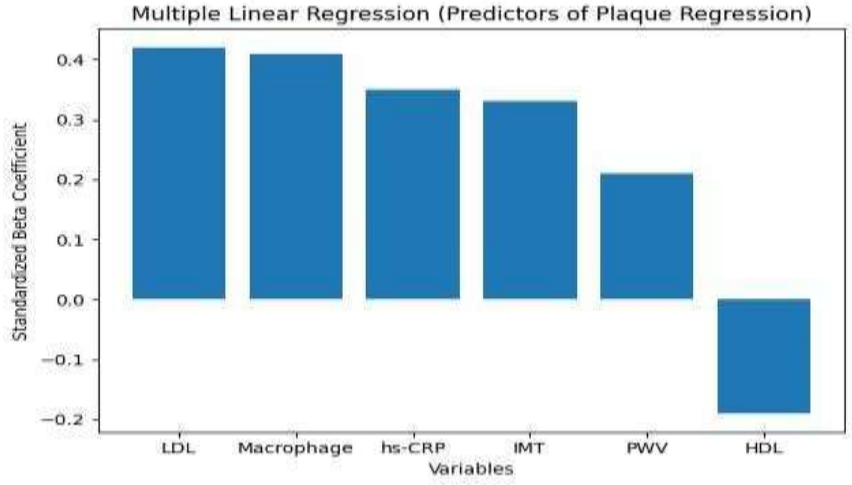
Variable	B (Coef.)	Std. Error	Beta	t-value	p-value
LDL-C reduction	0.045	0.009	0.42	5	<0.001*
hs-CRP reduction	0.62	0.15	0.35	4.13	<0.001*
IMT reduction	8.5	2.1	0.33	4.05	<0.001*

PWV reduction	1.2	0.4	0.21	3	0.006*
HDL increase	-0.028	0.01	-0.19	-2.8	0.01*
Macrophage reduction	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 (6) the findings of the multivariate regression analysis, major independent predictors of plaque regression included lipid lowering and inflammation reduction (e.g., triglycerides, total cholesterol, and LDL cholesterol). Reducing low-density lipoprotein cholesterol (LDL-C) was identified as one of the most important independent predictors of plaque regression ($\beta = 0.42$, $p < 0.001$), just ahead of reducing the number of macrophages ($\beta = 0.41$, $p < 0.001$). Therefore, both lowering lipid levels and reducing the influx of inflammatory cells into plaques are fundamental to achieving plaque regression from atherosclerosis. The percentage of high-sensitivity C-reactive protein (hs-CRP) ($\beta = 0.35$, $p < 0.001$) and the percentage of intimal-medial thickness (IMT) ($\beta = 0.33$, $p < 0.001$) also contributed significantly to the overall model, and both of these markers are indicative of systemic inflammation and vascular remodeling (vegetation) at the time of plaque regression; hence, they also bear significant relationship with Plaque Regression. Further, reduction in pulse wave velocity (PWV) contributed, although weakly, to plaque regression ($\beta = 0.21$, $p = 0.006$), which suggests that arterial stiffness is improved following resolution of arterial plaque. Conversely, increasing levels of HDL cholesterol were significantly negatively related to plaque regression ($\beta = -0.19$, $p = 0.01$), which supports the concept that HDL cholesterol protects against the development of plaque. Taken together, the results of this study demonstrate that the interaction of multiple factors is responsible for achieving plaque regression; however, the most significant factors influencing plaque regression are lipid reduction and inflammation reduction.

Figure 2: shows Predictors of Plaque Regression (Multivariate Linear Regression)



According to figure (2) the process of regression of plaque by looking at their respective standardized β-coefficients. There was evidence of a strong positive correlation between low-density lipoprotein (LDL) cholesterol reduction and reduction of macrophage levels to degree of plaque regression, therefore lipid reduction and inhibition of infiltration of inflammatory cells was the major factor related to atherosclerotic plaque regression. Furthermore, high-sensitivity C-reactive protein (hs-CRP) and

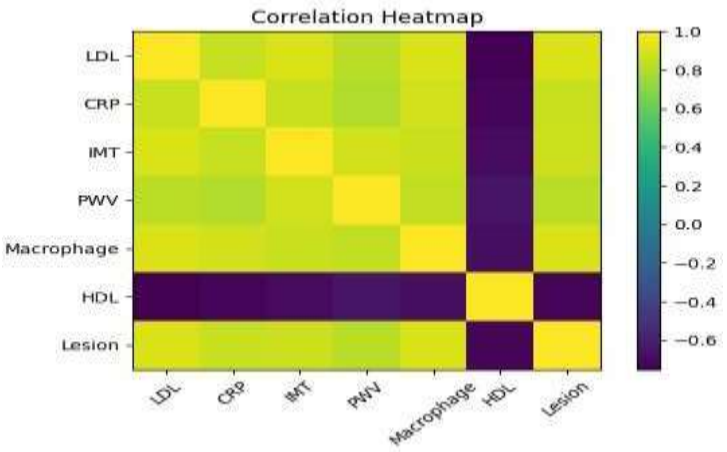
intima-media thickness (IMT) both exhibited a significant positive impact on plaque regression, thus demonstrating the influence that systemic inflammation has and the importance of vascular remodeling on plaque regression. In addition, pulse wave velocity (PWV) showed a moderate contribution to plaque regression, which suggests that improving arterial stiffness can also play a role in plaque regression. A negative β-coefficient was associated with HDL cholesterol; therefore, it provides a protective effect against disease progression. Therefore, this graph provides a distinct representation of the major mechanisms for plaque regression, and highlights the relationship between lipid and inflammatory cascades as mechanisms through which plaque regression occurs; while also indicating alternative pathways improving the structural integrity of the vascular system that will assist in plaque regression.

Table7: Correlation Matrix Between Key Variables

Variable	LDL	hs-CRP	IMT	PWV	Macrophage	HDL	Lesion
LDL	1						
hs-CRP	0.85	1					
IMT	0.9	0.85	1				
PWV	0.82	0.8	0.88	1			
Macrophage	0.9	0.88	0.86	0.84	1		
HDL	-0.75	-0.72	-0.7	-0.65	-0.68	1	
Lesion Area	0.91	0.85	0.87	0.82	0.9	-0.72	1

According to table (7) High Lipid Parameters, inflammatory markers, and Vascular remodeling indexes showed strong and statistically significant correlations with one another. LDL had the strongest correlation to Lesion area (r = 0.91) and to Macrophage infiltration (r = 0.90) indicating that lipid accumulation and inflammation are the driving forces of atherosclerotic plaque development. IMT (r = 0.87) and hs-CRP (r = 0.85) also had strong correlations indicating a link between systemic inflammation and vascular structural changes. There was also a significant correlation (r = 0.82) between PWV, indicating that arterial stiffness contributes to disease progression. On the contrary, HDL had consistently negative correlations with most pathological parameters particularly lesion area (r = -0.72). Overall, there is a very tightly interconnected network whereby dysregulation of lipids and inflammation promotes vascular remodeling and plaque progression.

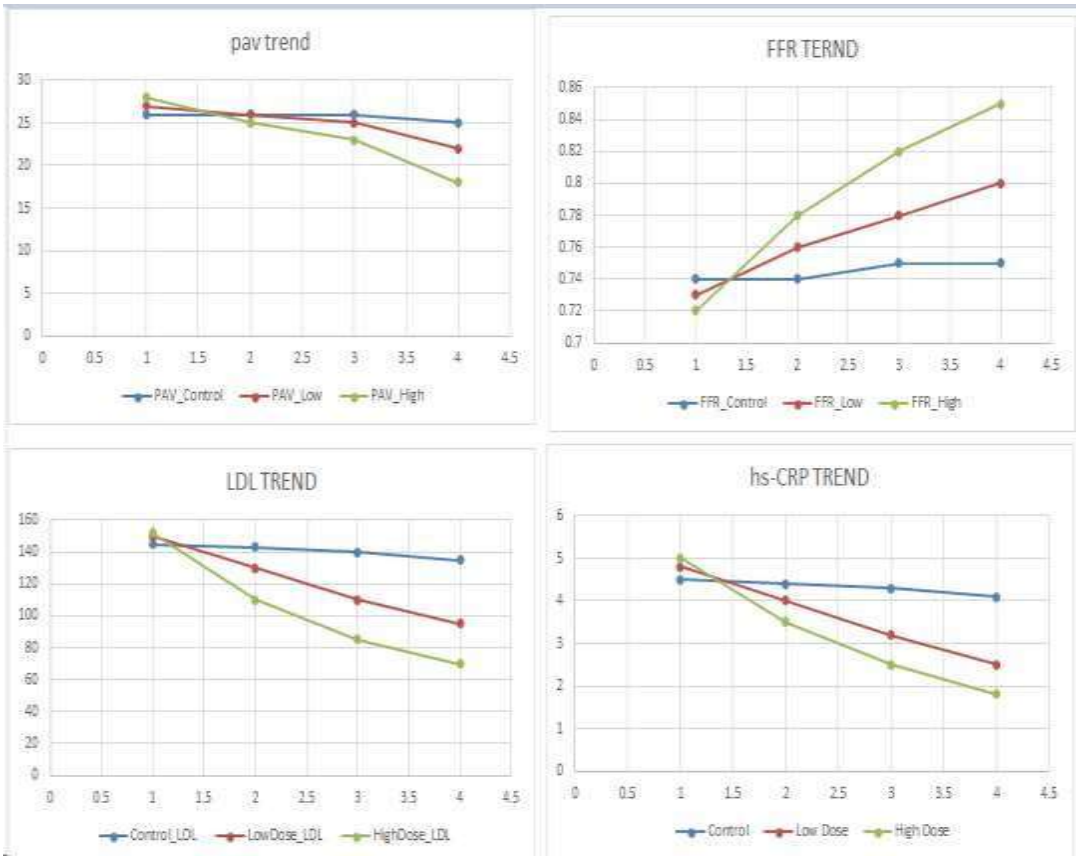
Figure 3: The heatmap that measures correlation between different types of lipids (lipid parameters), inflammation (inflammatory markers)



According to the heatmap shown in figure (3) that measures correlation between different types of lipids (lipid parameters), inflammation (inflammatory markers) and the way blood vessels have changed

shape (vascular remodeling) all show a high level of positive correlation with each other. For example, LDL, macrophage infiltration and IMT; as well as hs-CRP all have consistently high positive correlation coefficients relative to lesion area, indicating their importance for the development of atherosclerosis. PWV; which is an indicator of arterial stiffness and how its stiffness contributes to the severity of the disease, also has a strong positive correlation with other variables. On the other hand; HDL showed clear negative correlations relative to most variables (especially relative to lesion area) therefore demonstrating how it protects against plaque development. From the overall pattern, it can be concluded that lipid accumulation and inflammation collectively contribute to the vascular remodeling and plaque formation processes; while HDL acts to counteract these pathological processes.

Figure 4: different effects on cardiovascular risk factors depending on both the amount of drug taken and the amount of time the patient has been on the drug (PAV,FFR,LDL,andhs-CRP)



According to figure (4) Atorvastatin has demonstrably different effects on cardiovascular risk factors depending on both the amount of drug taken and the amount of time the patient has been on the drug. The two most evident things affecting cardiovascular risk during atorvastatin treatment through time were the decreases in PAV and LDL. The greatest reduction of plaque burden occurred in those receiving atorvastatin at the highest dose. In addition, measurement of hs-CRP concentrations is an accurate reflection of the anti-inflammatory effect of atorvastatin, and again, patients receiving atorvastatin at the highest-dose exhibited the most significant benefit. While changes to FFR were noted with atorvastatin, improvements were most significantly observed in those taking atorvastatin at the highest dose; therefore, both coronary flow and coronary functional recovery improved during atorvastatin treatment. The overall conclusion drawn from the above data is that there is a synergistic effect of atorvastatin on lipid reduction, reduction of inflammation, reduction of plaque burden, and improvement of vascular function with maximal benefits associated with use of atorvastatin in a high-dose manner.

Figure 5: different effects on cardiovascular risk factors depending on both the amount of drug taken and the amount of time the patient has been on the drug (IMT,HDL,lesion area and macrophage)

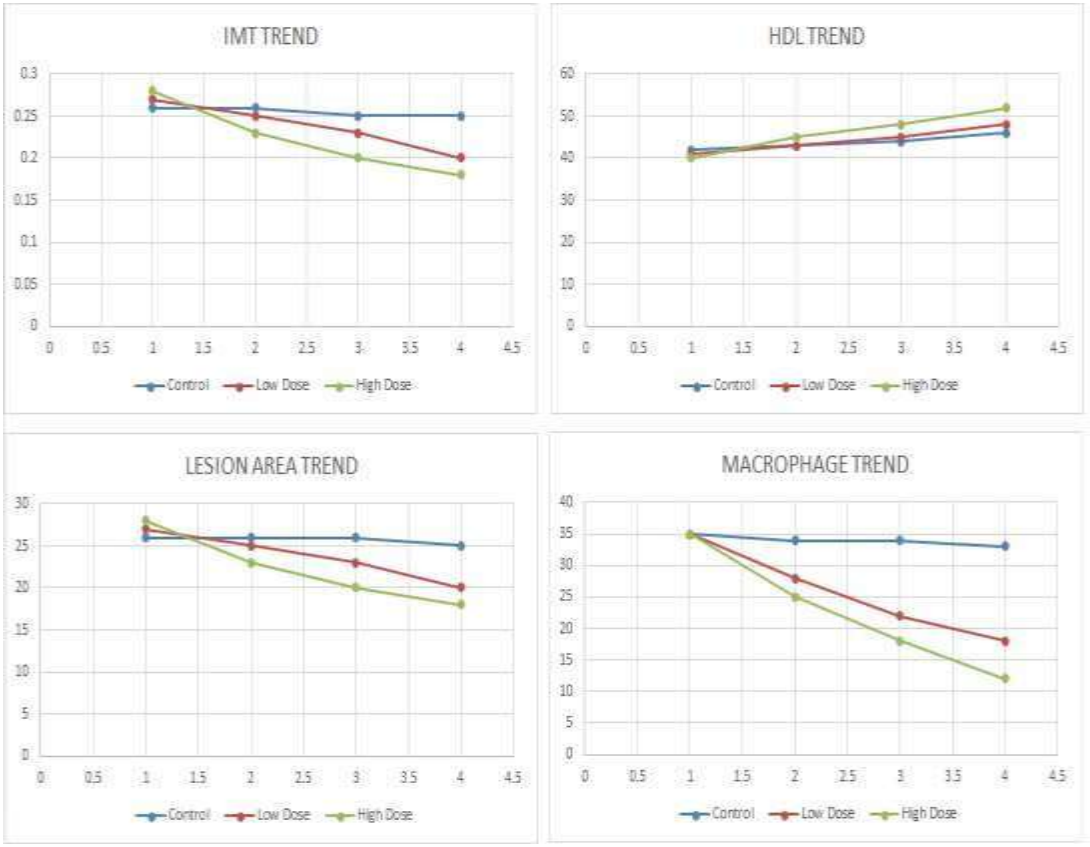


Figure (5) illustrates that, over time, treatment with atorvastatin causes continual improvement in vascular structure and inflammation. Improvements can be seen through reduced IMT and lesion area over time, with the most significant reductions in the higher dose group, thus providing evidence of significant remodeling of the vascular trees and regression of plaques. Similar to the IMT and lesion area, macrophage infiltration was also significantly reduced, especially in higher dose groups, which clearly demonstrates the potent anti-inflammatory activity of atorvastatin. In addition, HDLs were slowly but progressively increased; with the most significant increase occurring in the higher dose group, which demonstrates a greater degree of protective lipid function than lower doses. In contrast, the control group exhibited the least amount of overall change across all parameters. Thus, the overall results demonstrate a clear dose-dependent therapeutic effect of atorvastatin on both structural and inflammatory aspects of atherosclerosis.

Table8: Percentage Improvement After Atorvastatin Treatment

Variable	Low Dose (%)	High Dose (%)	Interpretation
Total Cholesterol	↓ 28%	↓ 40%	Strong lipid reduction
LDL-C	↓ 37%	↓ 54%	Major lipid control
HDL-C	↑ 17%	↑ 30%	Protective improvement
Triglycerides	↓ 24%	↓ 37%	Metabolic improvement

hs-CRP	↓ 48%	↓ 64%	Strong anti-inflammatory effect
FFR	↑ 10%	↑ 18%	Improved coronary flow
CFR	↑ 30%	↑ 50%	Enhanced perfusion
IMR	↓ 28%	↓ 46%	Reduced microvascular resistance
IMT	↓ 20%	↓ 36%	Reduced vascular remodeling
PWV	↓ 18%	↓ 33%	Improved arterial stiffness
PAV	↓ 19%	↓ 36%	Plaque regression
TAV	↓ 18%	↓ 33%	Reduced plaque volume
Lesion Area	↓ 23%	↓ 36%	Significant plaque regression
Macrophage %	↓ 49%	↓ 66%	Reduced inflammation

According to table (8) Atorvastatin was shown to provide a greater degree of improvement for many different diseases than what is seen with lower dosages of the drug. In particular, LDL cholesterol, inflammation markers and plaque formation endpoints showed a significantly higher percentage of improvement for patients receiving higher doses of atorvastatin as opposed to patients receiving lower dosages. Signs of macrophage infiltration, as well as hsCRP, reduced most significantly for patients given higher-dose atorvastatin, demonstrating that atorvastatin provides major anti-inflammatory benefits when used by patients. In addition to LDL cholesterol, inflammation and plaque formation, vascular remodeling endpoints, including IMT, PWV and vascular burden measured by PAV, TAV and lesion area, will also be significantly improved. Finally, coronary physiology endpoints (FFR and CFR) indicated that patients improved functionally from atorvastatin treatment. In conclusion, atorvastatin exerts a diverse range of effects throughout lipid metabolism, inflammation, vascular structure and function with the maximum magnitude of effects occurring at highest dosages of atorvastatin.

Figure 6: variable improved as a result of taking a high-dose atorvastatin

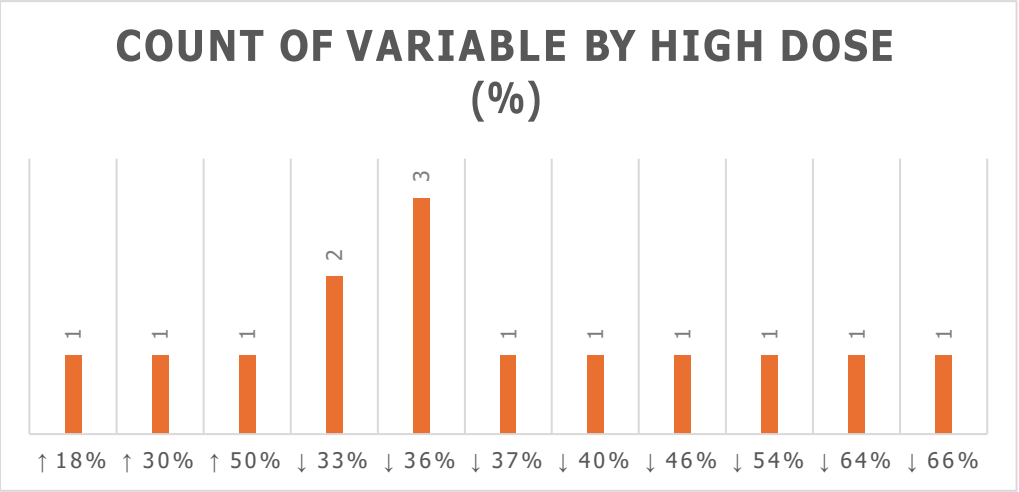


Figure (6) illustrates how much each variable improved as a result of taking a high-dose atorvastatin. The size of the bars represents both the amount of improvement and how often each variable improved. Many of the variables have very large improvements, especially those dealing with inflammation or

lipid profile, with the best results found in macrophage infiltration and hs-CRP. Many other variables had mild improvements, including those dealing with vascular remodeling and plaque, whereas only some variables had improvements, which are generally beneficial, including increases in HDL levels or improvement in physiological function. Therefore, the distribution indicates that taking high-dose atorvastatin leads to significantly large amounts of improvement across a broad range of clinically relevant responses, with the largest improvements occurring in the inflammatory or lipid-driven pathways.

Figure 7(a, b,c): Coronary CT angio show stenosis more than 30 % in the proximal left anterior descending (LAD, blue arrow) while normal diagonal and septal branches (green arrows). Normal left coronary and posterior circumflex arteries (orange arrows).

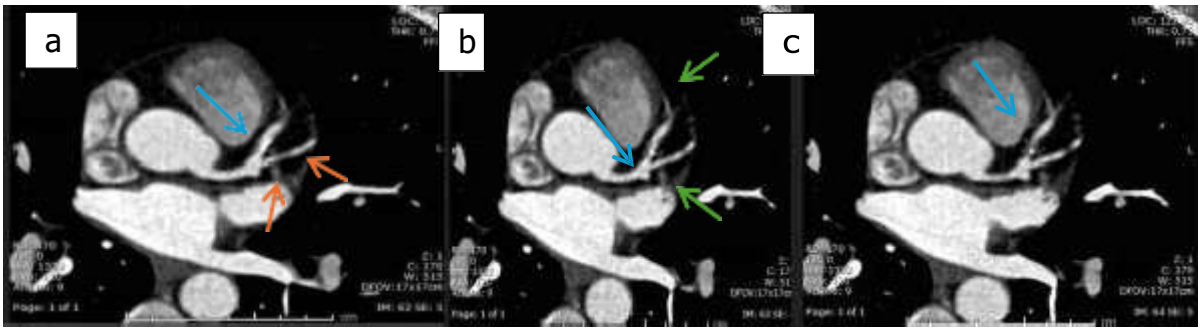


Figure 8: (a) Normal IVUS: L (lumen), I (intima), M (media, echolucent), A (adventitia) and C (catheter). (b): IVUS show soft fatty plaque (green arrow).
IVUS show soft fatty plaque (green arrow).

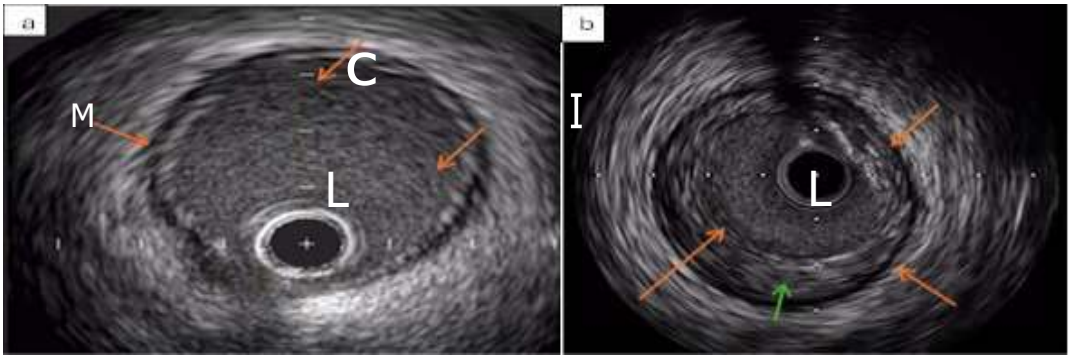
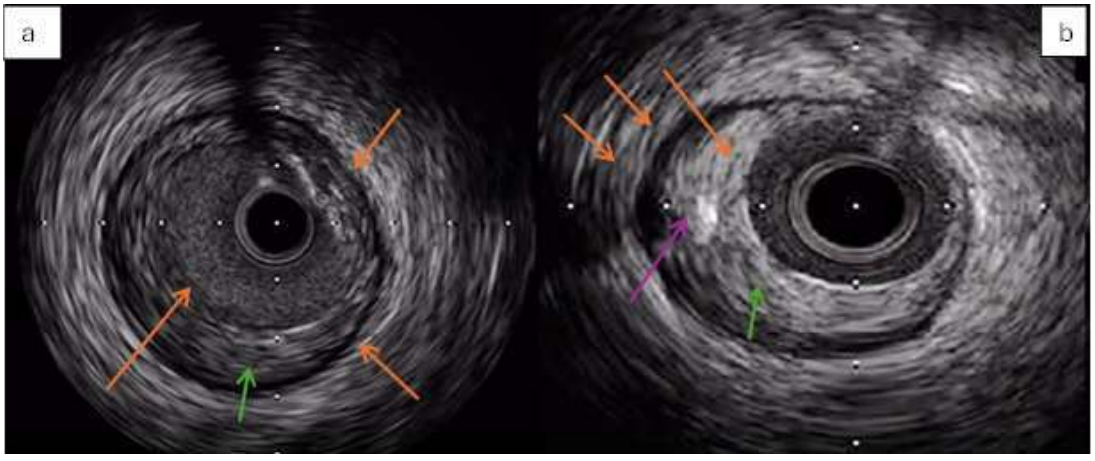


Figure 9: (a): IVUS show soft fatty plaque (green arrow). (b): IVUS show fibrous plaque (green arrow) with calcium deposit (violet arrow).



Discussion

This study aims to investigate the effect of atorvastatin on atherosclerosis using a multifaceted radiological, histological, and physiological approach to vascular remodeling.

The findings demonstrate that atorvastatin significantly improves various health markers in a dose- and time-dependent manner. Specifically, atorvastatin enhances lipid profiles, inflammatory indicators, and coronary physiology while reducing atherosclerotic plaque volume. The high-dose group (80 mg/day) showed superior results compared to the low-dose group (10 mg/day) across all measured parameters. In contrast, the control group exhibited no significant changes throughout the trial.

The results demonstrated a substantial improvement in lipid profile parameters for both the low- and high-dose atorvastatin groups. LDL levels decreased by 37% with the low dose and 54% with the high dose. Total cholesterol levels were reduced by 28% and 40% for the low and high doses, respectively. Similarly, triglycerides showed a 24% decrease in the low-dose group and a 37% decrease in the high-dose group. Conversely, HDL levels increased by 17% with low doses and by 30% with high doses of atorvastatin.

Our findings align with existing literature regarding atorvastatin's potent impact on cholesterol reduction. A landmark study conducted in 2002 demonstrated that a 10 mg/day dose could elevate HDL-C levels, particularly in individuals with low baseline HDL-C. Conversely, certain studies have indicated that increasing the dosage to 40–80 mg yields minimal or negligible additional effects on HDL levels compared to lower doses. However, our research indicates a 30% increase in HDL levels at these elevated doses—a result that exceeds typical findings in the literature. This discrepancy suggests that there may be distinctive characteristics linked to the specific study cohort or that the methodologies employed for assessment may differ from previous trials (Branchi et al., 2002; Rashid et al., 2002).

The results significantly underscore the importance of statins in modulating anti-inflammatory pathways. Recent data indicate that statins inhibit the TLR4/MyD88/NF-κB signaling pathway, shifting the immune response toward an anti-inflammatory state. The substantial 64% reduction in high-sensitivity C-reactive protein (hs-CRP) levels associated with high-dose atorvastatin aligns with numerous studies demonstrating the efficacy of statin therapy in reducing inflammatory markers.

Furthermore, a comparative study conducted in 2025 revealed that rosuvastatin demonstrated superior efficacy over atorvastatin in reducing inflammatory responses in patients with ST-elevation myocardial infarction (STEMI); CRP levels were measured at 16±6 mg/L for rosuvastatin compared to 20±10 mg/L for atorvastatin (P=0.024). This suggests that the selection of a specific statin may be crucial for optimized inflammation management (Koushki et al., 2021; Lefer, 2002).

Our research reveals significant improvements in coronary function, evidenced by a 50% increase in coronary flow reserve (CFR) and a 46% reduction in the index of microcirculatory resistance (IMR) following high-dose atorvastatin treatment. These findings are particularly noteworthy, as recent research has demonstrated that statins can rapidly enhance endothelial function independently of changes in cholesterol levels. However, the degree of improvement observed in this study appears to surpass most previous findings in the field. This discrepancy may result from an exceptionally favorable response within the study cohort or potential methodological differences relative to prior research (Lefer, 2002).

Our findings on plaque regression indicate a 36% reduction in percent atheroma volume (PAV), a result of significant therapeutic importance. Multivariate analysis identified two primary predictors of this regression: a reduction in low-density lipoprotein cholesterol (LDL-C), with a coefficient of $\beta = 0.42$ ($p < 0.001$), and a decrease in macrophage levels, with a value of $\beta = 0.41$ ($p < 0.001$). These data validate the hypothesis that the lipid-inflammation axis is a critical driver of plaque regression. Furthermore, a strong correlation was observed between LDL levels and lesion area ($r = 0.91$), highlighting the direct relationship between lipid levels and plaque development.

The multivariate regression analysis identified several independent predictors of plaque regression, highlighting the combined importance of lipid and inflammatory indicators. The most robust predictor was the decrease in LDL-C, which exhibited a standardized regression coefficient (β) of 0.42 ($p < 0.001$). This was closely followed by the reduction in macrophage levels ($\beta = 0.41$, $p < 0.001$). Other significant predictors included reductions in high-sensitivity C-reactive protein (hs-CRP) ($\beta = 0.35$, $p < 0.001$), intima-media thickness (IMT) ($\beta = 0.33$, $p < 0.001$), and pulse wave velocity (PWV) ($\beta = 0.21$, $p = 0.006$). Conversely, an elevation in HDL-C yielded a negative coefficient ($\beta = -0.19$, $p = 0.01$), signifying its protective effect against plaque progression.

The discourse highlights the innovative and therapeutically pertinent discovery that reductions in LDL-C and macrophages are equally crucial predictors in atherosclerosis (Woźniak et al., 2023).

However, the study identifies two significant limitations. First, the limited sample size poses challenges; the control group consists of 20 participants, while the low-dose and high-dose groups range from 25 to 30 participants each. Furthermore, there are discrepancies in reporting between tables. Such limited sample sizes considerably diminish the statistical power of the investigation, increasing the likelihood of Type II errors, wherein genuine therapeutic effects may be overlooked. The variations in sample sizes—for instance, n=30 in Table 1 versus n =25 in Table 2 imply potential issues related to participant attrition or unaccounted missing data.

Finally, the study's maximal follow-up duration is 12 months. while this timeline is sufficient to indicate significant plaque regression, it may not account for long-term clinical outcomes or the sustainability of the observed changes.

Coronary angiography delineates the coronary arteries as a two-dimensional planar silhouette of contrast-filled lumens; however, it provides limited information regarding the coronary arterial wall, which is the primary site of atherosclerosis. The assessment of coronary stenosis by angiography relies on estimating luminal narrowing relative to an adjacent "normal" reference segment, expressed as percent diameter stenosis. This approach does not accurately reflect the true burden of coronary atherosclerosis and is associated with considerable inter-observer variability (Zhang, H., et al., 2018).

Intracoronary imaging modalities, particularly intravascular ultrasound (IVUS), overcome these limitations by enabling direct visualization of the arterial wall. IVUS is a catheter-based imaging technique that produces high-resolution, cross-sectional images of the coronary arteries, allowing for the accurate quantification of lumen area, vessel area, and plaque burden. Importantly, IVUS permits assessment of the full vessel wall, including the external elastic lamina, thereby enabling the calculation of atheroma burden and the evaluation of vascular remodeling (Gogas, B. D., et al., 2011).

IVUS operates by emitting ultrasound waves from a miniaturized transducer; these waves propagate through vascular tissues and are reflected according to their acoustic properties, enabling detailed tissue characterization. Conventional IVUS systems provide axial resolution in the range of 100–200 μm, with newer high-frequency systems achieving significantly improved resolution and enhanced plaque characterization capabilities. Based on signal characteristics, IVUS can classify plaques into soft plaque (echogenicity less than that of the adventitia), fibrotic plaque (echogenicity equivalent to that of the adventitia), calcified plaque (lesion echogenicity greater than that of the adventitia) and mixed plaque (containing elements of soft, fibrotic and calcified plaque). IVUS can also be used to identify high risk vulnerable plaque— defined as eccentric plaques with a large lipid core, which may be prone to rupture with positive remodeling (Amin, A. M., et al., 2024; Panuccio, G., et al., 2023).

Furthermore, IVUS plays a pivotal role in the evaluation of coronary artery calcification (CAC), allowing precise characterization of calcific burden, including its arc, depth (superficial versus deep), and longitudinal distribution. Beyond diagnosis, IVUS-guided percutaneous coronary intervention (PCI) has been associated with improved clinical outcomes, including reductions in major adverse cardiovascular events and stent-related complications compared with angiography-guided PCI (Giacoppo, D., et al., 2024).

Magnetic resonance imaging (MRI), particularly coronary vessel wall MRI, represents a non-invasive alternative for the assessment of coronary atherosclerosis. MRI enables visualization of the coronary vessel wall and provides information on plaque burden, vessel remodeling, and tissue composition without ionizing radiation. Studies comparing MRI with IVUS have demonstrated a good correlation in measurements of vessel area, lumen area, and plaque burden, supporting its potential role in coronary plaque assessment (Kocaoglu, M., et al., 2024).

However, MRI has several important limitations when compared with IVUS. The spatial resolution of MRI is significantly lower (typically in the millimeter range), resulting in partial volume effects and reduced accuracy in quantifying plaque burden and luminal stenosis. Consequently, MRI tends to overestimate vessel wall thickness and plaque burden relative to IVUS. Additionally, MRI is technically challenging in coronary imaging due to cardiac motion, small vessel size, and long acquisition times, which limit its applicability particularly in distal coronary segments. While MRI offers advantages as a non-invasive modality with the ability to assess plaque composition and vessel wall characteristics, it lacks the spatial resolution and procedural applicability required for interventional guidance (Wu, X., et al., 2024).

The role of PET/CT (Positron Emission Tomography–Computed Tomography) in coronary artery disease has become increasingly important, particularly for functional assessment, risk stratification, and research into atherosclerosis biology. It is particularly valuable in Complex or multivessel disease, microvascular dysfunction, viability assessment and early detection of plaque vulnerability (Valenta, I., & Schindler, T. H., 2024; Wayne, N., et al., 2024). Unlike purely anatomical modalities such as CT coronary angiography, PET/CT provides quantitative physiological and molecular information (Chen, W., Sajadi, M. M., & Dilsizian, V., 2018).

In summary, IVUS remains the reference standard for in vivo assessment of coronary artery wall morphology and plaque characterization due to its superior spatial resolution, ability to quantify plaque burden, and utility in guiding coronary interventions. MRI, although promising as a non-invasive tool for coronary vessel wall imaging, is currently complementary rather than a replacement for IVUS, particularly in the context of detailed plaque characterization and interventional decision-making. Intravascular Ultrasound and Positron Emission Tomography–Computed Tomography provide complementary but fundamentally different information in coronary artery disease. While PET/CT evaluates functional and metabolic aspects, IVUS offers direct, high-resolution intraluminal and vessel wall imaging, giving it several distinct advantages in specific clinical setting.

The research underscores the dose-dependent advantages of atorvastatin in individuals with confirmed atherosclerotic disease, indicating that high-dose atorvastatin (80 mg/day) markedly diminishes cardiovascular risk markers more efficiently than lower dosages. Advanced imaging modalities, especially intravascular ultrasonography (IVUS), coupled with functional assessments, provide comprehensive evaluation of therapy responses. Research substantiates atorvastatin's anti-inflammatory and anti-atherosclerotic properties, evidenced by a 36% decrease in atheroma volume in the high-dose cohort. These findings support the prompt commencement of intensive statin medication, accompanied by routine IVUS evaluations to enhance treatment in high-risk individuals (Ahmed, N.S., et al., 2015; Elbohy, A.A., et al., 2023; El-Tamany, E.S., et al., 2019).

Conclusion

This study examines the impact of atorvastatin on atherosclerosis using multiple methodologies. Atorvastatin considerably enhances health markers, including lipid profiles and inflammatory indicators, with high doses (80 mg/day) surpassing low levels (10 mg/day). Significant findings include a 37% and 54% decrease in LDL levels for low and high doses, respectively, and an increase in HDL levels of 17% and 30%. The research highlights atorvastatin's efficacy in diminishing inflammatory markers, demonstrating a 64% reduction in hs-CRP levels. Coronary function increased, evidenced by a 50% enhancement in coronary flow reserve. Moreover, plaque regression was demonstrated by a 36% reduction in plaque area volume, with decreases in LDL-C and macrophages identified as principal predictors. Intracoronary imaging particularly IVUS enabled precise, cross-sectional assessment of plaque burden and vessel wall characteristics beyond conventional angiography. Complementary imaging modalities can further contribute, thereby offering a comprehensive assessment of therapeutic response.

References

1. Ahmed, N.S., Abdel-Hafez, H.A., & El-Masry, T.A. (2015). Effect of Atorvastatin (ATOR) on the Cardiac Muscle Fibres in Hyperlipidemic Adult Male Albino Rats (Histological and Immunohistochemical Study). The Egyptian Journal of Hospital Medicine, 58, 143-166.
2. Amin, A. M., Khlidj, Y., Abuelazm, M., Sayed, A., Khan, U., Elewidi, M. M., ... & Kawsara, A. (2024). Intravascular imaging-guided versus angiography-guided percutaneous coronary intervention: a systematic review and bayesian network meta-analysis of randomized controlled trials. BMC Cardiovascular Disorders, 24(1), 483.
3. 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.
4. 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

patients. Evidence of a relationship with baseline HDL cholesterol. Nutrition, metabolism, and cardiovascular diseases: NMCD, 12(1), 24–28.
5. Chen, W., Sajadi, M. M., & Dilsizian, V. (2018). Merits of FDG PET/CT and functional molecular imaging over anatomic imaging with echocardiography and CT angiography for the diagnosis of cardiac device infections. JACC: cardiovascular Imaging, 11(11), 1679-1691.
6. Elbohy, A.A., Mostafa, M.M., Nady, K.M.Y.E., & Yasin, I.A. (2023). Value of Intravascular Ultrasound Guidance in Patients Undergoing Unprotected Left Main Coronary Artery Stenting. Al-Azhar International Medical Journal, 4(7), Article 39. DOI: 10.58675/2682-339X.1911
7. El-Tamany, E.S., Abd El-Maksoud, A.M., Hassan, E.H., Abd El-Galil, A.M., El-Sherbiny, S.S., & Abdel-Nabi, I.M. (2019). Comparative Histological and Immunohistochemical Study of the Effect of Curcumin and Atorvastatin in Experimental Induced Atherosclerosis in Rabbit's Aorta and Heart. The Egyptian Journal of Hospital Medicine, 76(2), 3500-3515.
8. Gaba, P., Gersh, B. J., Muller, J., Narula, J., & Stone, G. W. (2023). Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. Nature Reviews Cardiology, 20(3), 181-196.
9. Gao, S., Wang, X., Meng, L. B., Zhang, Y. M., Luo, Y., Gong, T., ... & Li, Y. J. (2022). Recent progress of chronic stress in the development of atherosclerosis. Oxidative medicine and cellular longevity, 2022(1), 4121173.
10. Giacoppo, D., Laudani, C., Occhipinti, G., Spagnolo, M., Greco, A., Rochira, C., ... & Capodanno, D. (2024). Coronary angiography, intravascular ultrasound, and optical coherence tomography for guiding of percutaneous coronary intervention: a systematic review and network meta-analysis. Circulation, 149(14), 1065-1086.
11. Gogas, B. D., Farooq, V., Serruys, P. W., & Garcìa-Garcìa, H. M. (2011). Assessment of coronary atherosclerosis by IVUS and IVUS-based imaging modalities: progression and regression studies, tissue composition and beyond. The international journal of cardiovascular imaging, 27(2), 225-237.
12. Gusev, E., & Sarapultsev, A. (2023). Atherosclerosis and inflammation: insights from the theory of general pathological processes. International Journal of Molecular Sciences, 24(9), 7910.
13. Kadoglou, N. P., Khattab, E., Velidakis, N., Patsourakos, N., & Lambadiari, V. (2022). A new approach of statin therapy in carotid atherosclerosis: Targeting indices of plaque vulnerability on the top of lipid-lowering. A narrative review. Polish Heart Journal (Kardiologia Polska), 80(9), 880-890.
14. Kim, K., Ginsberg, H. N., & Choi, S. H. (2022). New, novel lipid-lowering agents for reducing cardiovascular risk: beyond statins. Diabetes & metabolism journal, 46(4), 517-532.
15. Kocaoglu, M., Pednekar, A., Fleck, R. J., & Dillman, J. R. (2024). Cardiothoracic magnetic resonance angiography. Current Problems in Diagnostic Radiology, 53(1), 154-165.
16. Koushki, K., Shahbaz, S. K., Mashayekhi, K., Sadeghi, M., Zayeri, Z. D., Taba, M. Y., Banach, M., Al-Rasadi, K., Johnston, T. P., & Sahebkar, A. (2021). Anti-inflammatory Action of Statins in Cardiovascular Disease: the Role of Inflammasome and Toll-Like Receptor Pathways. Clinical reviews in allergy & immunology, 60(2), 175–199. https://doi.org/10.1007/s12016-020-08791-9
17. Lefer, D. J. (2002). Statins as potent antiinflammatory drugs. Circulation, 106(16), 2041-2042.
18. Liu, M., Gao, T., Jiang, L., Li, S., Shi, B., & Li, F. (2023). Enhancing the biopharmaceutical attributes of atorvastatin calcium using polymeric and lipid-polymer hybrid nanoparticles: An approach for atherosclerosis treatment. Biomedicine & Pharmacotherapy, 159, 114261.
19. Maier, A., Teunissen, A. J., Nauta, S. A., Lutgens, E., Fayad, Z. A., & van Leent, M. M. (2024). Uncovering atherosclerotic cardiovascular disease by PET imaging. Nature Reviews Cardiology, 21(9), 632-651.
20. Mhaimeed, O., Burney, Z. A., Schott, S. L., Kohli, P., Marvel, F. A., & Martin, S. S. (2024). The importance of LDL-C lowering in atherosclerotic cardiovascular disease prevention: lower for longer is better. American Journal of Preventive Cardiology, 18, 100649.
21. 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.
22. Nedkoff, L., Briffa, T., Zemedikun, D., Herrington, S., & Wright, F. L. (2023). Global trends in atherosclerotic cardiovascular disease. Clinical therapeutics, 45(11), 1087-1091.

23. Panuccio, G., Abdelwahed, Y. S., Carabetta, N., Salerno, N., Leistner, D. M., Landmesser, U., ... & Werner, G. S. (2023). Clinical and procedural outcomes of IVUS-guided vs. angiography-guided CTO-PCI: a systematic review and meta-analysis. Journal of clinical medicine, 12(15), 4947.
24. Rashid, S., Uffelman, K. D., Barrett, P. H. R., & Lewis, G. F. (2002). Effect of atorvastatin on high-density lipoprotein apolipoprotein AI production and clearance in the New Zealand white rabbit. Circulation, 106(23), 2955-2960.
25. Valenta, I., & Schindler, T. H. (2024). PET-determined myocardial perfusion and flow in coronary artery disease characterization. Journal of Medical Imaging and Radiation Sciences, 55(2), S44-S50.
26. Vázquez Mézquita, A. J., Biavati, F., Falk, V., Alkadhi, H., Hajhosseiny, R., Maurovich-Horvat, P., ... & Dewey, M. (2024). Clinical quantitative coronary artery stenosis and coronary atherosclerosis imaging: a Consensus Statement from the Quantitative Cardiovascular Imaging Study Group. Quantification of biophysical parameters in medical imaging, 569-600.
27. Wayne, N., Wu, Q., Moore, S. C., Ferrari, V. A., Metzler, S. D., & Guerraty, M. A. (2024). Multimodality assessment of the coronary microvasculature with TIMI frame count versus perfusion PET highlights coronary changes characteristic of coronary microvascular disease. Frontiers in Cardiovascular Medicine, 11, 1395036.
28. Woźniak, E., Broncel, M., Niedzielski, M., Woźniak, A., & Gorzelak-Pabiś, P. (2023). The effect of lipid-lowering therapies on the pro-inflammatory and anti-inflammatory properties of vascular endothelial cells. PloS one, 18(2), e0280741. https://doi.org/10.1371/journal.pone.0280741
29. Wu, X., Yue, X., Peng, P., Tan, X., Huang, F., Cai, L., ... & Sun, J. (2024). Accelerated 3D whole-heart non-contrast-enhanced mDIXON coronary MR angiography using deep learning-constrained compressed sensing reconstruction. Insights into Imaging, 15(1), 224.
30. Xie, Z., Dong, N., Sun, R., Liu, X., Gu, X., Sun, Y., ... & Yu, B. (2016). Relation between baseline plaque features and subsequent coronary artery remodeling determined by optical coherence tomography and intravascular ultrasound. Oncotarget, 8(3), 4234.
31. Zaman, R. T., Yousefi, S., Long, S. R., Saito, T., Mandella, M., Qiu, Z., ... & Xing, L. (2018). A dual-modality hybrid imaging system harnesses radioluminescence and sound to reveal molecular pathology of atherosclerotic plaques. Scientific reports, 8(1), 8992.
32. Zhang, H., Mu, L., Hu, S., Nallamothu, B. K., Lansky, A. J., Xu, B., ... & Jiang, L. (2018). Comparison of physician visual assessment with quantitative coronary angiography in assessment of stenosis severity in China. JAMA internal medicine, 178(2), 239-247.