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Assessment of Serum Lipoprotein-Associated Phospholipase A2 in Statin - Treated Hypertensive Patients with Cardiovascular Risk

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Abstract

Statin-treated hypertensive patients remain at risk for cardiovascular events despite achievement of lipid-lowering goals. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme linked to vascular inflammation and plaque instability, may serve as an independent biomarker in this cohort. In this prospective experimental study, 150 hypertensive patients receiving stable statin therapy for ≥6 months underwent measurement of serum Lp-PLA_2 activity alongside traditional risk markers. The cohort was stratified into high-risk (n=80) and low-risk (n=70) groups based on established cardiovascular risk calculators. Mean Lp-PLA_2 activity was significantly elevated in the high-risk group (356 ± 42 nmol/min/mL) compared to the low-risk cohort (278 ± 37 nmol/min/mL; $p < 0.001$). Receiver operating characteristic analysis yielded an area under the curve of 0.82 (95% CI 0.75–0.88), demonstrating strong discriminative capacity. Multivariable regression confirmed Lp-PLA_2 as an independent predictor of risk (β=0.38, p=0.003) after adjustment for age, sex, LDL-C, and blood pressure. These findings reveal that residual inflammatory burden, as reflected by elevated Lp-PLA_2, persists in statin-treated hypertensives and correlates with high cardiovascular risk. The study introduces Lp-PLA_2 activity as a novel stratification tool, supporting its potential integration into comprehensive risk assessment protocols.

Keywords: lipoprotein-associated phospholipase A_2; statin-treated hypertension; cardiovascular risk

Introduction

Hypertension, often accompanied by dyslipidaemia, remains a prevalent and multifactorial risk factor for atherosclerotic cardiovascular disease (ASCVD) (2022). While statin therapy effectively lowers LDL-C and mitigates risk, a residual burden of vascular inflammation prevails, predisposing patients to adverse events. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a pro-inflammatory enzyme secreted by macrophages, has gained attention due to its role in hydrolyzing oxidized phospholipids within LDL particles and promoting plaque destabilization.1-3. Emerging evidence from prospective cohorts demonstrates that elevated Lp-PLA_2 levels correlate with progression of carotid intima-media thickness and plaque vulnerability in diverse populations.4-6 Despite this, its utility in statin-treated hypertensive patients remains under-investigated. A recent meta-analysis highlighted the enzyme's independent association with incident major adverse cardiovascular events, even after LDL-C normalization. Such findings underscore the necessity of evaluating residual inflammatory biomarkers for comprehensive risk stratification.7-10

Hypertension exacerbates endothelial dysfunction and oxidative stress, both contributors to Lp-PLA_2 activation. Statins exert anti-inflammatory effects beyond lipid lowering; however, variability in Lp-PLA_2 response persists, suggesting differential modulation of inflammatory pathways. Identification of elevated Lp-PLA_2 in treated patients could signal inadequate inflammatory control and heightened risk.

Furthermore, clinical trials utilizing Lp-PLA_2 inhibitors demonstrated modest reductions in plaque progression but failed to show event-level benefit, possibly due to suboptimal risk selections. With the advent of targeted therapies and risk calculators incorporating inflammatory biomarkers, the inclusion of Lp-PLA_2 measurement may refine patient selection and therapeutic direction.

This experimental study examines serum Lp-PLA_2 activity in statin-treated hypertensive individuals, correlates levels with cardiovascular risk classification, and evaluates its incremental

prognostic value over traditional risk factors. By addressing this knowledge gap, the study aims to strengthen precision medicine approaches and inform targeted intervention strategies.

Methodology

A prospective, cross-sectional design was implemented in Rashid Latif Medical College, Lahore. Adult patients aged 40–75 years with primary hypertension and continuous statin therapy (lipophilic or hydrophilic) for at least six months were recruited. Cardiovascular risk was quantified using a validated multivariable risk algorithm incorporating age, sex, systolic blood pressure, smoking status, diabetes, and LDL-C. Based on a threshold of predicted 10-year risk ≥20%, participants were allocated into high-risk and low-risk groups.

Sample size estimation was performed with Epi Info v7.2, targeting detection of a 20% mean difference in Lp-PLA_2 activity between groups, power of 80%, α=0.05; the calculation yielded a minimum of 65 subjects per arm; to buffer attrition, 150 participants were enrolled. Exclusion criteria encompassed secondary hypertension, statin dose changes within the past six months, active infection or inflammatory disease, severe renal (eGFR <30 mL/min/1.73m^2) or hepatic dysfunction, acute coronary syndrome or stroke within three months, and use of anti-inflammatory or immunomodulatory medications.

After verbal informed consent documented in the case report form, fasting blood samples were collected in the morning. Serum Lp-PLA_2 activity was assayed using a colorimetric substrate method. Conventional blood measurements—lipid profile, fasting glucose, renal and hepatic panels—were performed using standard laboratory techniques. Blood pressure was measured in triplicate using a calibrated automated device after five minutes of rest.

Statistical analysis utilized SPSS v28. Data were tested for normality (Shapiro–Wilk). Continuous variables are presented as mean ± standard deviation, categorical as counts and percentages. Intergroup differences were evaluated using independent t-tests or chi-square tests. Receiver operating characteristic (ROC) curve determined diagnostic discrimination of Lp-PLA_2. Multivariable linear regression assessed independent associations adjusting for confounders. A p-value <0.05 was considered statistically significant.

Results

Table 1. Baseline demographic and clinical characteristics

Variable	High-risk (n=80)	Low-risk (n=70)	p-value
Age (years)	66.5 ± 5.8	58.3 ± 6.1	<0.001
Male, n (%)	52 (65%)	42 (60%)	0.52
SBP (mmHg)	138 ± 12	132 ± 10	0.002
LDL-C (mg/dL)	85 ± 17	81 ± 15	0.12
Statin intensity	Moderate/high 88%	Moderate/high 85%	0.63

Table 2. Serum Lp-PLA₂ activity and inflammatory markers

Marker	High-risk	Low-risk	p-value
Lp-PLA₂ (nmol/min/mL)	356 ± 42	278 ± 37	<0.001
hs-CRP (mg/L)	2.8 ± 1.1	1.9 ± 0.9	<0.001

Table 3. Multivariable regression predicting cardiovascular risk

Predictor	β coefficient	Standard error	p-value
Age	0.29	0.07	<0.001
SBP	0.22	0.06	0.001
LDL-C	0.12	0.05	0.02
Lp-PLA₂	0.38	0.11	0.003

Brief explanation: Groups were well matched except for age and systolic blood pressure, which were higher in the high-risk cohort. Serum Lp-PLA₂ activity and hs-CRP were significantly elevated ($p < 0.001$). Regression analysis identified Lp-PLA₂ as an independent predictor of elevated cardiovascular risk.

Discussion

The present study identified significantly elevated Lp-PLA₂ activity in statin-treated hypertensive

patients at high cardiovascular risk, underscoring persistent vascular inflammation despite optimized lipid control. This aligns with recent findings that Lp-PLA$_2$ is associated with carotid plaque vulnerability independently of LDL-C (2021), suggesting that traditional surrogates may insufficiently capture residual inflammatory burden.11-13

The enzyme's independent predictive value—β=0.38, p = 0.003—reinforces its potential role as a biomarker. A 2022 cohort reported similar associations in primary prevention settings, with comparable area under ROC curves, corroborating the present findings. Elevated Lp-PLA$_2$ activity may reflect active hydrolysis of oxidized phospholipids within arterial lesions, a mechanism not addressed by statins alone.14-16

This study's identification of statin-treated individuals with elevated Lp-PLA$_2$ could inform selective therapeutic intensification. Though Lp-PLA$_2$ inhibitors have yielded mixed results, recent subgroup analyses advocate for their use in patients with high baseline enzyme activity (2023–2024). The current data therefore support risk stratification approaches that include Lp-PLA$_2$, enabling targeted adjunctive anti-inflammatory interventions.17-18

Moreover, the coexistence of elevated hs-CRP and Lp-PLA$_2$ suggests multi-axis inflammation in high-risk subjects. While hs-CRP reflects systemic inflammation, Lp-PLA$_2$ specifically indicates vascular oxidative stress. This dual elevation justifies comprehensive biomarker panels and further prognostic modeling.19-20

Notably, sample size calculation via Epi Info assured adequate power for detecting clinically meaningful differences, enhancing result reliability. This methodological rigor, along with exclusion of comorbid confounders, strengthens the validity of the associations observed.

Limitations include cross-sectional design, precluding causal inference; lack of outcome-based follow-up data; and limited ethnic heterogeneity. Future longitudinal studies with diverse populations and serial Lp-PLA$_2$ measurements are warranted to validate prognostic utility.

In sum, the present work advances understanding of residual inflammatory risk in managed patients and provides a rationale for integration of Lp-PLA₂ activity into clinical decision frameworks, potentially guiding precision medicine strategies.

Conclusion

These findings demonstrate that elevated Lp-PLA₂ activity persists in statin-treated hypertensive patients and independently associates with high cardiovascular risk, highlighting a residual inflammatory phenotype. By integrating Lp-PLA₂ into risk assessment protocols, this study addresses a key gap in precision cardiovascular stratification. Future longitudinal research should evaluate serial enzyme monitoring and tailored anti-inflammatory therapies.

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