



## LIPID PROFILE AND STATIN THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION AND ACUTE ISCHEMIC STROKE RECEIVING ANTI-COAGULANT THERAPY

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### ABSTRACT

**Purpose:** To evaluate the association of lipid profile and statin therapy with stroke severity and early functional outcome in anticoagulated patients with atrial fibrillation (AF) hospitalized with acute ischemic stroke (IS).

**Materials and methods:** This prospective, single-center cohort study included consecutive patients with acute IS and documented AF who were receiving oral anticoagulant therapy prior to stroke onset, including direct oral anticoagulants or vitamin K antagonists with therapeutic INR values. Demographic characteristics, comorbidities, lipid profile, and clinical risk scores were recorded on admission. Stroke severity was assessed using the NIHSS, and early functional outcome was evaluated using the modified Rankin Scale at discharge.

**Results:** A total of 55 patients were included (median age 79 years; 40% male). Prior statin therapy was identified in 40% of patients. Patients receiving statins had significantly lower LDL-C levels at admission. However, no significant differences were observed between statin-treated and non-treated patients regarding stroke severity, early functional outcome, or in-hospital mortality. Notably, statin-treated patients exhibited a higher baseline clinical risk profile, reflected by higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores and a greater prevalence of prior IS.

**Conclusion:** In anticoagulated patients with AF presenting with acute IS, lipid profile and statin therapy were not primary determinants of early stroke severity or functional outcome. Comparable outcomes among statin-treated patients despite a higher baseline risk suggest that dyslipidemia may influence the clinical course of IS in a more indirect manner. This single-center study highlights the need for further investigation to clarify the role of lipid-related mechanisms beyond anticoagulation.

**Keywords:** Atrial fibrillation, stroke, anticoagulant therapy, statins, lipids,

### INTRODUCTION

Atrial fibrillation (AF) remains one of the leading risk factors for ischemic stroke (IS), significantly increasing the risk of thromboembolic cerebrovascular events [1]. Current clinical guidelines emphasize the central role of oral anticoagulants, including direct oral anticoagulants (DOACs) and vitamin K antagonists, in both primary and secondary prevention of stroke in patients with AF [2]. Nevertheless, despite optimal anticoagulant therapy, a proportion of patients with AF continue to experience IS, underscoring the need to identify additional mechanisms and risk factors contributing to residual cerebrovascular risk.

Elevated levels of low-density lipoprotein cholesterol (LDL-C) are a well-established risk factor for cardiovascular disease, including IS [3]. While lipid abnormalities play a clearly defined role in the pathophysiology of atherothrombotic stroke, their relevance in cardioembolic stroke associated with AF remains less well characterized [4]. Over recent decades, lipid-lowering therapy, particularly statins, has demonstrated substantial benefits in both primary and secondary stroke prevention [3, 5]. Beyond their LDL-C-lowering effects, statins exert pleiotropic effects, including improved endothelial function, inhibition of platelet activation, anti-inflammatory effects, and reduction of tissue factor expression, all of which may contribute to a reduction in thrombotic risk [6, 7].

To date, clinical studies have yielded conflicting results regarding the relationship between lipid profile, statin therapy, and stroke risk in patients with AF. Some investigations suggest a higher risk of cardioembolic events in the presence of unfavorable lipid ratios, such as a high HDL-C/LDL-C ratio, as well as an association between intensive lipid control with high-dose statin therapy and a reduced risk of ischemic stroke in anticoagulated patients [8, 9]. In contrast, other studies have failed to demonstrate a significant association between LDL-C levels and residual IS risk in patients with AF receiving anticoagulant therapy [10]. Consistent with these findings, hyperlipidemia is not included as a risk factor in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score used for stroke risk stratification in AF patients [2, 11]. These contradictory observations highlight the need for further studies to clarify the role of dyslipidemia and statin therapy

in determining stroke severity and clinical outcomes among patients with AF who experience IS despite effective anticoagulation. In this context, the present study aims to evaluate the association between lipid profile and statin therapy, on the one hand, and stroke severity and early functional outcome, on the other, in patients with AF receiving effective anticoagulant treatment and hospitalized with acute IS.

## MATERIALS AND METHODS

### Study design

The prospective cohort study was conducted over a one-year period at the Neurology Clinic of University Hospital Dr Georgi Stranski, Plevna, Bulgaria. Consecutive patients hospitalized with acute IS and documented AF were enrolled. All included patients had been receiving oral anticoagulant therapy prior to the index stroke event.

### Study population

Eligible participants were adults aged  $\geq 18$  years with acute IS confirmed by clinical presentation and neuroimaging studies, and with AF (paroxysmal, persistent, or permanent) documented either prior to or at the time of hospital admission. All patients were on oral anticoagulant therapy before stroke onset, including DOACs (apixaban, rivaroxaban, dabigatran, or edoxaban) or vitamin K antagonists (acenocoumarol). Patients treated with vitamin K antagonists were included only if the international normalized ratio (INR) was within the therapeutic range ( $\geq 2.0$ ).

Statin therapy was defined as treatment initiated prior to the occurrence of the index IS and was identified at hospital admission based on history and available medical documentation. Patients were classified into two groups according to statin exposure: those receiving statin therapy prior to stroke onset and those not receiving statins.

### Data collection

For each patient, demographic data (age and sex), clinical characteristics, and comorbid conditions were collected, including arterial hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure, previous stroke, renal impairment, and liver disease.

Laboratory investigations were performed upon admission and included lipid profile parameters - total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides.

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission and at discharge. Early functional outcome was evaluated at discharge using the modified Rankin Scale (mRS). An unfavorable early functional outcome was defined as an mRS score  $\geq 3$ . In-hospital mortality was recorded as an additional outcome measure. For each patient, thromboembolic risk was assessed using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and bleeding risk was evaluated using the HAS-BLED score.

### Statistical methods

Descriptive statistics were presented as median and interquartile range (IQR) for continuous variables and as absolute numbers and percentages for categorical variables. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the  $\chi^2$

test or Fisher's exact test for categorical variables, as appropriate.

Statistical significance was defined as a p-value  $< 0.05$ . All statistical analyses were conducted using appropriate statistical software.

### Ethical considerations

The study protocol was approved by the Ethics Committee of the Medical University of Plevna. All data were processed in accordance with applicable data protection regulations and analyzed in anonymized form.

## RESULTS

A total of 55 patients (n=55) with acute IS and AF who had been receiving oral anticoagulant therapy prior to stroke onset were included in the study. The median age of the cohort was 79 years (IQR 76–84), and 22 patients (40.0%) were male.

Forty-nine patients (89.1%) were treated with direct oral anticoagulants, while six patients (10.9%) were receiving vitamin K antagonists with documented therapeutic INR values. Reduced doses of DOACs were administered in 24 patients (43.6%). Statin therapy prior to stroke onset was identified in 22 patients (40.0%).

The most common comorbid conditions were arterial hypertension, present in 50 patients (90.9%), ischemic heart disease in 27 patients (49.1%), congestive heart failure in 21 patients (38.2%), and diabetes mellitus in 17 patients (30.9%). A history of previous ischemic stroke was documented in 18 patients (32.7%).

The median CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 5 (IQR 4–6), while the median HAS-BLED score was 2 (IQR 2–3). Admission lipid profile showed median LDL-C levels of 2.47 mmol/L (IQR 1.89–2.82), HDL-C levels of 1.19 mmol/L (IQR 0.98–1.46), and triglyceride levels of 1.38 mmol/L (IQR 0.98–1.77).

Stroke severity assessed by the NIHSS at admission had a median score of 7 (IQR 5–13). Among the 51 patients who survived to discharge, the median NIHSS score at discharge was 4 (IQR 2–9). Early functional outcome assessed using the modified Rankin Scale at discharge showed a median mRS score of 3 (IQR 2–4), with an unfavorable early functional outcome (mRS  $\geq 3$ ) observed in 29 patients (52.7%). In-hospital mortality occurred in four patients, corresponding to a rate of 7.3%.

**Table 1.** Detailed demographic, clinical and laboratory characteristics of the study population (n=55).

Clinical characteristic	Value
Age, years, median (IQR)	79 (76-84)
Male sex, n (%)	22 (40.0)
Direct oral anticoagulant (DOAC), n (%)	49 (89.1)
Vitamin K antagonist (VKA), n (%)	6 (10.9)
Reduced-dose anticoagulation, n (%)	24 (43.6)
Statin therapy, n (%)	22 (40.0)
Arterial hypertension, n (%)	50 (90.9)
Ischemic heart disease, n (%)	27 (49.1)

Heart failure, n (%)	21 (38.2)
Diabetes mellitus, n (%)	17 (30.9)
Prior ischemic stroke, n (%)	18 (32.7)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, median (IQR)	5 (4-6)
HAS-BLED score, median (IQR)	2 (2-3)
LDL-C, mmol/l, median (IQR)	2.47 (1.89-2.82)
HDL-C, mmol/l, median (IQR)	1.19 (0.98-1.46)
Triglycerides, mmol/l, median (IQR)	1.38 (0.98-1.77)
NIHSS on admission, median (IQR)	7 (5-13)
NIHSS at discharge*, median (IQR)	4 (2-9)
mRS at discharge, median (IQR)	3 (2-4)
mRS e <sup>3</sup> , n (%)	29 (52.7)
In-hospital mortality, n (%)	4 (7.3)

\*NIHSS at discharge available for 51 patients.

Patients were stratified into two groups according to statin exposure prior to stroke onset: those receiving statin therapy (statin (+), n = 22) and those not receiving statins (statin (-), n = 33). Median age did not differ sig-

nificantly between the two groups, being 79.5 years (IQR 76.3-82.8) in the statin (+) group and 78.0 years (IQR 75-85) in the statin (-) group.

Admission lipid profile demonstrated lower LDL-C levels in patients receiving statin therapy, with a median LDL-C of 1.97 mmol/L (IQR 1.28-2.57), compared with 2.54 mmol/L (IQR 2.22-3.10) in patients not receiving statins. Median HDL-C levels were 1.10 mmol/L (IQR 0.96-1.33) in the statin (+) group and 1.30 mmol/L (IQR 1.07-1.57) in the statin (-) group.

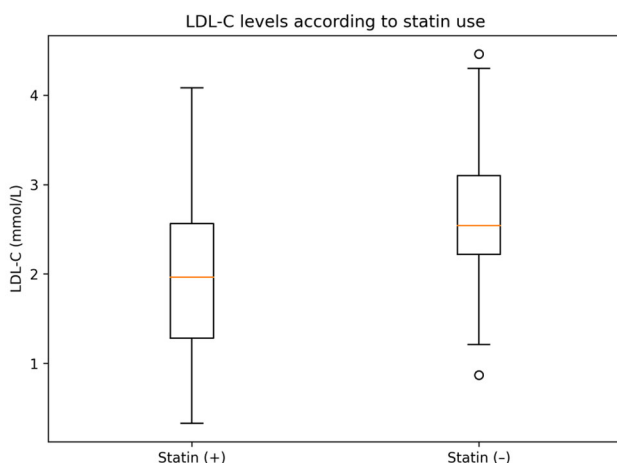
Stroke severity at admission, assessed using the NIHSS, was lower in the statin (+) group, with a median score of 6.5 (IQR 5-11.8), compared with 8 (IQR 5-16) in patients not receiving statin therapy. Early functional outcome assessed by the mRS at discharge showed a more favorable trend among patients receiving statins, with a median mRS score of 2.5 (IQR 2.0-4.0), compared with 3.0 (IQR 2.0-5.0) in the statin (-) group. Patients in the statin (+) group exhibited a higher baseline clinical risk profile, reflected by higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and a higher prevalence of prior ischemic stroke.

**Table 2.** Comparison according to statin use.

Variable	Statin group (n=22)	No statin group (n=33)	p-value
Age, median (IQR), years	79.5 (76.3–82.8)	78 (75–85)	ns
Male sex, n (%)	9 (40.9)	13 (39.4)	ns
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, median (IQR)	6 (5–7)	5 (4–6)	<0.05
HAS-BLED score, median (IQR)	3 (2–3)	2 (1–2)	<0.05
Previous ischemic stroke, n (%)	10 (45.5)	8 (24.2)	ns
LDL-C, mmol/L, median (IQR)	1.97 (1.28–2.57)	2.54 (2.22–3.1)	<0.01
HDL-C, mmol/L, median (IQR)	1.10 (0.96–1.33)	1.3 (1.07-1.57)	ns
NIHSS on admission, median (IQR)	6.5 (5–11.8)	8 (5–16)	ns
mRS at discharge, median (IQR)	2.5 (2–4)	3 (2–5)	ns
In-hospital mortality, n (%)	1 (4.5)	3 (9.1)	ns

Data are presented as median (interquartile range) or number (percentage); ns – not significant (p ≥0.05)

**Fig. 1.** LDL-C levels according to statin use.



LDL cholesterol levels in patients receiving statin therapy and those without statin therapy. The boxes represent the interquartile range, the horizontal line indicates the median, and whiskers denote the minimum and maximum values.

## DISCUSSION

Intensive lowering of LDL-C levels through statin therapy is a well-established effective strategy for reducing the risk of atherothrombotic vascular events. Multiple studies have demonstrated a strong association between dyslipidemia and the risk of IS, particularly in atherosclerotic subtypes [4, 5, 11, 12]. In contrast, cardioembolic stroke in patients with AF is characterized by a distinct pathophysiological mechanism, primarily

involving thrombus formation within the left atrium and subsequent embolization to the cerebral circulation, rather than progressive arterial atherosclerosis [13, 14].

Within this context, the role of lipid profile as a direct determinant of IS risk and severity in patients with AF remains less clearly defined. Several clinical studies have failed to demonstrate a significant association between LDL-C levels and the risk or severity of IS in anticoagulated patients with AF [6, 9, 10]. These observations suggest that, once effective anticoagulation is achieved, lipid-related mechanisms may play a limited role in the clinical expression of acute cardioembolic stroke.

The results of this prospective cohort study demonstrate that patients receiving statin therapy prior to stroke onset had significantly lower LDL-C levels, but no corresponding difference in stroke severity as assessed by the NIHSS, early functional outcome measured by the mRS, or in-hospital mortality. Taken together, these findings support the notion that, in anticoagulated patients with AF, lipid profile and statin therapy are not primary determinants of early clinical outcome following acute IS.

Notably, statin-treated patients exhibited a higher baseline clinical burden, reflected by higher CHA, DS, -VASc and HAS-BLED scores, a greater prevalence of prior ischemic stroke. The absence of worse outcomes in this group raises the possibility of a risk-modifying or “neutralizing” effect of statins, potentially mediated by a pleiotropic mechanism independent of lipid lowering.

These findings are biologically plausible given the known anti-inflammatory, endothelial-stabilizing, and antithrombotic effects of statins [7, 15, 16, 17]. These mechanisms may contribute to improved vascular function and a reduction in residual thromboembolic risk in patients with AF, even when effective anticoagulant therapy is administered [18, 19, 20].

The absence of hyperlipidemia as a component of the CHA, DS, -VASc risk score further reflects the prevailing clinical understanding that thromboembolic risk in AF is primarily driven by demographic and clinical factors rather than lipid status [11, 15]. In this pathophysiological framework, the findings of the present study appear consistent and coherent, suggesting that dyslipidemia and statin therapy exert a modifying rather than determining influence on early stroke severity and functional outcome in anticoagulated patients with AF.

These observations highlight the multifactorial nature of residual cerebrovascular risk in AF patients and

suggest that the relationship between lipid profile, statin therapy, and stroke outcomes may be more complex. Further research in larger multicenter cohorts is needed to better characterize these associations in patients with AF.

#### Limitations

Several limitations of the present study should be considered when interpreting the results. First, the single-center design and the relatively small sample size limit the statistical power of the analysis and restrict the generalizability of the findings to broader patient populations. Second, the observational nature of the study precludes causal inferences regarding the relationship between statin therapy, lipid profile, and clinical outcomes; therefore, the observed associations should be regarded as hypothesis-generating.

In addition, lipid profile was assessed only at hospital admission, without information on long-term lipid control or adherence to statin therapy prior to stroke onset. The study also did not include stratification according to statin intensity or duration of treatment, factors that may have influenced clinical outcomes. Finally, functional outcome was evaluated exclusively during the early in-hospital period, without long-term follow-up, thereby limiting the assessment of potential delayed effects of statin therapy. The limited sample size further reduces the ability to detect moderate but clinically meaningful differences between the study groups.

#### CONCLUSION

In patients with AF who experience acute IS despite effective anticoagulation, lipid profile and prior statin therapy do not appear to be primary determinants of stroke severity and early functional outcome. However, the absence of worse outcomes among statin-treated patients with a higher baseline risk suggests that these factors may influence the clinical course of IS in a more indirect manner. This exploratory single-center study with a limited sample size highlights the complexity of residual cerebrovascular risk in AF and underscores the need for further investigation to clarify the role of lipid-related mechanisms beyond anticoagulation.

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## REFERENCES:

1. Shweikialrefae B, Ko DT, Fang J, Pang A, Austin PC, Dorian P, et al. Statin Use and Stroke Rate in Older Adults With Atrial Fibrillation: A Population Based Cohort Study. *J Am Heart Assoc.* 2023 Jun 20;12(12):e028381. [PubMed]
2. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2024 Sep 29;45(36):3314–414. [PubMed]
3. Lee M, Cheng CY, Wu YL, Lee JD, Hsu CY, Ovbiagele B. Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention: A Meta-analysis of Randomized Clinical Trials. *JAMA Neurol.* 2022 Apr 1;79(4):349. [PubMed]
4. Hindy G, Engström G, Larsson SC, Traylor M, Markus HS, Melander O, et al. Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes: A Mendelian Randomization Study. *Stroke.* 2018 Apr;49(4):820–7. [PubMed]
5. Cholesterol Treatment Trialists' (Ctt) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomized trials. *The Lancet.* 2010 Nov;376(9753):1670–81. [PubMed]
6. Ding WY, Proty MB, Davies IG, Lip GYH. Relationship between lipoproteins, thrombosis, and atrial fibrillation. *Cardiovasc Res.* 2022 Feb 21;118(3):716–31. [PubMed]
7. Phillip Owens A, Mackman N. The Antithrombotic Effects of Statins. *Annu Rev Med.* 2014 Jan 14;65(1):433–45. [PubMed]
8. Soler-Espejo E, Chen Y, Rivera-Caravaca JM, Ramos-Bratos MP, Esteve-Pastor MA, Marín F, et al. Relation of the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio to residual risk in anticoagulated patients with atrial fibrillation: a report from the prospective Murcia AF Project III cohort. *Cardiovasc Diabetol.* 2025 Sep 30;24(1):374. [PubMed]
9. Ip B, Yip T, Hung T, Yam TF, Yeung C, Ko H, et al. Lipid control and stroke risk in atrial fibrillation patients treated with direct oral anticoagulants and statins. *Eur Stroke J.* 2025 Mar;10(1):137–44. [PubMed]
10. Omelchenko A, Hornik-Lurie T, Gabay H, Minha S, Assali A, Pereg D. LDL Cholesterol and Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation. *Am J Med.* 2021 Apr;134(4):507–13. [PubMed]
11. Lane DA, Lip GYH. Use of the CHA<sub>2</sub> DS<sub>2</sub> -VASC and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation. *Circulation.* 2012 Aug 14;126(7):860–5. [PubMed]
12. Yuan S, Tang B, Zheng J, Larsson SC. Circulating Lipoprotein Lipids, Apolipoproteins and Ischemic Stroke. *Ann Neurol.* 2020 Dec;88(6):1229–36. [PubMed]
13. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* 1993 Jan;24(1):35–41. [PubMed]
14. Castellano JM, Chinitz J, Willner J, Fuster V. Mechanisms of Stroke in Atrial Fibrillation. *Card Electrophysiol Clin.* 2014 Mar;6(1):5–15. [PubMed]
15. Undas A, Brummel-Ziedins KE, Mann KG. Anticoagulant effects of statins and their clinical implications. *Thromb Haemost.* 2014;112(03):392–400. [PubMed]
16. Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniadis C, Stefanadis C. Innate and Adaptive Inflammation as a Therapeutic Target in Vascular Disease. *J Am Coll Cardiol.* 2014 Jun;63(23):2491–502. [PubMed]
17. Huang T, Yap L, Chen C, Lin H, Lin S, Li Y. Long Term Statin Use Is Associated With Reduced Rates of Adverse Events in Patients With Newly Diagnosed Atrial Fibrillation. *J Am Heart Assoc.* 2024 Dec 17;13(24):e035827. [PubMed]
18. Ding WY. Residual Stroke Risk in Atrial Fibrillation. *Arrhythmia Electrophysiol Rev.* 2021 Oct 27; 10(3):147–53. [PubMed]
19. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Stroke.* 2012 Dec;43(12):3298–304. [PubMed]
20. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol.* 2015 Apr;12(4):230–43. [PubMed]

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