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Research article

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Retrospective analysis of statin use and arteriovenous fistula thrombosis in hemodialysis: Is there a dose-dependent effect?

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Abstract. *Arteriovenous fistula (AVF) thrombosis is a major vascular access complication in hemodialysis (HD) patients, contributing to increased morbidity. Statins, known for their pleiotropic effects, may reduce AVF thrombosis risk, but evidence on dose-dependent effects is limited. This study evaluated the association between statin use, dose intensity, and AVF thrombosis in HD patients.*
Methods. A multicenter, retrospective cohort study was conducted using data from 562 HD patients with native AVFs across 10 dialysis clinics (May 2021–April 2025). Patients were categorized by statin use (users vs. non-users) and dose intensity (moderate vs. high vs. none). The primary outcome was AVF thrombosis; death was treated as a competing event. Kaplan-Meier survival curves and Fine and Gray subdistribution hazard models, adjusted for age, diabetes, dialysis vintage, Kt/V, glucose, calcium, blood flow, and pre-HD cardiovascular disease, were used to assess thrombosis risk.
Results. Of 562 patients (median follow-up 59 months), 212 (37.7%) were statin users. AVF thrombosis occurred in 54 (9.6%) patients, with 11 (7.1%) in statin users vs. 43 (10.6%) in non-users ($p = 0.006$). Kaplan-Meier analysis showed lower thrombosis probability in statin users (log-rank $p = 0.001$), with high-intensity users having the lowest risk ($p = 0.004$). In the unadjusted Fine and Gray model, high-intensity statins were associated with reduced thrombosis risk (sHR 0.61, 95% CI 0.59–0.97, $p = 0.03$), with a significant dose-dependent trend ($p = 0.018$). The adjusted model showed no significant association (moderate: sHR 0.67, $p = 0.16$; high: sHR 0.57, $p = 0.26$).
Conclusions. Statin use, particularly high-intensity, may reduce AVF thrombosis risk in HD patients, with a dose-dependent trend in unadjusted analyses. However, adjusted results were non-significant, possibly due to limited events. Larger prospective studies are needed to confirm these findings and optimize statin therapy for vascular access preservation.
Key words: *hemodialysis, arteriovenous fistula, thrombosis, statins, risk, treatment.*

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Ретроспективний аналіз застосування статинів та тромбозу артеріовенозної фістули у пацієнтів, які лікуються гемодіалізом: чи існує дозозалежний ефект?

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Резюме. *Тромбоз артеріовенозної фістули (АВФ) є основним ускладненням судинного доступу у пацієнтів, які лікуються методом гемодіалізу (ГД). Статини, відомі своєю плейотропною дією, можуть зменшити ризик тромбозу АВФ, але докази щодо дозозалежних ефектів обмежені. Метою дослідження було оцінити зв'язок між застосуванням статинів, інтенсивністю призначеної дози та тромбозом АВФ у ГД пацієнтів.*

Методи. До цього багатоцентрового ретроспективного когортного дослідження залучено дані 562 пацієнтів з хронічною хворобою нирок V стадії та нативною АВФ, які лікувались методом ГД у 10 діалізних центрах з травня 2021–по квітень 2025. Пацієнтів класифікували за прийомом статинів (група статинів і група без статинів) та інтенсивністю призначеної дози (помірна проти високої проти жодної). Первинною кінцевою точкою був тромбоз АВФ; летальний випадок розглядався як конкуруюча подія. Для оцінки ризику тромбозу використовували криві виживаності Каплан-Мейєра та моделі суброзподілу ризиків Файна-Грея, скориговані з урахуванням віку, діабету, тривалості діалізу, Kt/V, рівня глюкози, кальцію, швидкості кровотоку та наявності серцево-судинних подій перед початком ГД.

Результати. Серед 562 включених у дослідження ГД пацієнтів 212 (37,7%) приймали статини. Протягом 5 років спостереження, тромбоз АВФ діагностовано у 54 (9,6%) пацієнтів, серед яких 11 (7,1%) у пацієнтів групи статинів та у 43 (10,6%) хворих без терапії статинами (p = 0,006). Аналіз Каплана-Мейєра продемонстрував нижчу ймовірність тромбозу у пацієнтів, які отримували статини (log-rank p = 0,001), з найнижчим ризиком за прийому інтенсивної дози (p = 0,004). У нескоригованій моделі Файна та Грея прийом високої дози статинів асоціювався зі зниженим ризиком тромбозу (sHR 0,61, 95% CI 0,59–0,97, p = 0,03), зі значною дозозалежною тенденцією (p = 0,018). Скоригована модель не виявила суттєвого зв'язку між дозою статинів та ризиком тромбозу АВФ (помірна доза: sHR 0,67, p = 0,16; висока: sHR 0,57, p = 0,26).

Висновки. Застосування статинів, зокрема у високих дозах, асоційовано зі зниженням ризику тромбозу АВФ у ГД пацієнтів із дозозалежною тенденцією за результатами нескоригованого аналізу. Проте, після коригування на супутні фактори ці результати втратили статистичну значущість, що може бути зумовлено обмеженою кількістю подій. Для підтвердження цих даних та визначення оптимальної стратегії застосування статинів з метою збереження судинного доступу необхідні проспективні дослідження з залученням більшої когорти пацієнтів.

Ключові слова: *гемодіаліз, артеріовенозна фістула, тромбоз, статини, ризик, лікування.*

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Introduction. Arteriovenous fistulas (AVF) is the gold standard for vascular access in patients undergoing maintenance hemodialysis (HD), offering superior long-term patency and lower infection and complication rates compared to grafts and central venous catheters [1]. However, AVF thrombosis remains a major

clinical challenge, causing access failure, hospitalizations, the need for repeated interventions or surgical revisions, and contributing to increased all-cause and cardiovascular mortality [1, 2]. The identification of modifiable risk factors and prevention strategies to reduce the incidence of AVF thrombosis is, therefore, of critical importance to improving dialysis outcomes and preserving vascular access longevity.

Statins, widely prescribed for their lipid-lowering effects in cardiovascular disease (CVD) prevention [3-5], have also been shown to exert various pleiotropic effects, including anti-inflammatory, antithrombotic, and endothelial-stabilizing properties [6-8]. These mechanisms suggest a theoretical benefit of statins in maintaining AVF patency. Despite this biological plausibility, clinical evidence regarding the impact of statins on vascular access outcomes in HD patients remains limited and inconclusive [9-11].

Importantly, the role of lipid-lowering therapy in patients undergoing HD remains controversial. Major randomized controlled trials, such as 4D, AURORA, and SHARP, have demonstrated either modest or non-significant cardiovascular benefits of statin therapy in patients with end-stage kidney disease (ESKD) [12-14]. As a result, guidelines recommend selective and cautious statin use in this population, especially when initiated after the start of dialysis [15]. Although some recent large-scale observational studies have reported improved survival in statin users [16, 17], these findings do not specifically address vascular access outcomes and there is a general lack of data on the association between lipid-lowering therapy and the risk of AVF thrombosis in patients undergoing HD. Moreover, most available studies do not stratify results by statin dose and no consensus exists regarding whether higher-intensity statin therapy offers additional vascular access protection in HD patients.

Therefore, the present study aimed to evaluate the association between statin use and the risk of AVF thrombosis among patients receiving maintenance HD. Specifically, we sought to investigate whether higher statin doses are associated with a lower incidence of AVF thrombosis, independent of other known risk factors.

Methods. *Study design and setting*. This was a multicenter, retrospective cohort study conducted using data from a network of «Nephrocenter» dialysis clinics across six regions of Ukraine. The study included all patients receiving maintenance HD at 10 clinics, representing both urban and rural centers located in the Kyiv, Lviv, Odesa, Zaporizhzhia, Rivne, and Khmelnytskyi regions. The study period spanned from May 2021 to April 2025. Due to the retrospective design and use of de-identified patient data, the requirement for informed consent was waived by the institutional review board.

Study population. Adult patients (≥18 years) with ESKD receiving maintenance HD via AVF were eligible for inclusion. Patients were required to have been on HD for at least 3 months and to have complete medical records regarding medication history, vascular access events, and relevant clinical data. Other inclusion criteria were:

- Patients with a documented native AVF as the primary vascular access, used for at least 3 months, with no prior history of AVF failure or thrombosis before the start of follow-up.
- Availability of lipid profile data.
- Recorded information on statin use, including type, dose, and prescribing time (before or after HD initiation).
- Use of heparin anticoagulation during HD sessions, either as unfractionated heparin or low-molecular-weight heparin.

Exclusion criteria included:

- Use of arteriovenous grafts or central venous catheters as the primary vascular access.
- History of kidney transplantation during the study period.
- Incomplete records for statin use or lipid profiles.
- Known hypercoagulable disorders, active malignancy, use of antiplatelet or anticoagulant therapy on non-dialysis days, or the use of non-standard anticoagulation protocols during HD sessions (e.g., citrate anticoagulation or sessions without anticoagulation).

HD was performed using Fresenius 5008 dialysis machines, with high-flux dialyzers and bicarbonate-based dialysate. Standard treatment prescriptions involved three sessions per week, each lasting 4 hours, with blood flow rates typically ranging from 300 to 350 mL/min, adjusted individually based on vascular access function. The primary treatment goal was to achieve dialysis adequacy following international guidelines, targeting a single-pool Kt/V of ≥1.2. Dialysis adequacy and vascular access performance were regularly monitored as part of routine care.

Data collection. Data were extracted from electronic medical records across participating centers and included the following categories:

- Demographic and clinical variables: Age, sex, dialysis vintage at study enrollment, smoking and alcohol use status, presence of diabetes mellitus, history of cardiovascular disease (CVD) before HD initiation and during the dialysis period, CVD-related and non-CVD-related hospitalizations.
- Dialysis treatment parameters: Blood flow rate, ultrafiltration rate, and single-pool Kt/V values.
- Laboratory markers: Hemoglobin (Hb), C-reactive protein (CRP), serum calcium, phosphate, intact parathyroid hormone (iPTH), ferritin, and serum albumin levels.
- Lipid profile: Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and the atherogenic index of plasma (AIP).

- Statin use: Documented at the time of HD initiation or during follow-up, including the specific statin type and dosage.

Pre-HD CVD history was defined as any diagnosed non-fatal CVD event (e.g., myocardial infarction, stroke, heart failure, or coronary artery disease) recorded in the patient's medical history before HD initiation. Post-HD initiation CVD history was identified through medical records during the follow-up period and included new or recurrent events such as myocardial infarction, stroke, or heart failure. CVD-related hospitalization was defined as any admission with a primary diagnosis of a CVD condition, while non-CVD-related hospitalizations encompassed admissions for non-CVD causes (e.g., infections, gastrointestinal issues), as documented in hospital records.

To ensure data accuracy and completeness, patient records were cross-checked, and duplicate entries were removed. Patients with more than 5% missing data were excluded from the analysis. Data were collected at two time points: at the baseline and the last available follow-up before the study endpoint or completion.

Statin dosage classification. Statin use was determined based on electronic prescription records and confirmed by chart review. For baseline characteristics, the patients were classified into statins users and non-users. For dose-dependent analysis, the patients were divided into three groups: non-users, moderate-intensity-dose statin users, and high-intensity dose statin users. Statin intensity classification followed guidelines from the American College of Cardiology/American Heart Association (Table 1) [18].

Table 1

Statin Dosing and ACC/AHA Classification of Intensity

Statin	Moderate-intensity dosage	High-intensity dosage
Atorvastatin	10 to 20 mg	40 to 80 mg
Rosuvastatin	5 to 10 mg	20 to 40 mg
Simvastatin	20 to 40 mg	NA

Primary and secondary endpoints. The primary outcome was the incidence of primary AVF thrombosis in HD patients receiving statin therapy compared to those not receiving statins. AVF thrombosis was defined as a documented event of AVF failure due to clot formation requiring intervention (e.g., thrombectomy, angioplasty) or necessitating alternative vascular access. The secondary endpoint was the association of AVF thrombosis with statin dosage.

Statistical analysis. All statistical analyses were performed using MedCalc® Statistical Software version 23.1.3 (MedCalc Software Ltd, Ostend, Belgium), except for the Fine and Gray subdistribution hazard model, which was conducted using XLSTAT (Lumivero, 2025). Descriptive statistics were used to summarize patient characteristics across statin exposure groups. Continuous variables were assessed for normality using the Shapiro-Wilk test. Variables with normal distribution are presented as mean and standard deviation (M ± SD) and compared using the independent t-test or analysis of variance (ANOVA), as appropriate. Non-normally distributed data are presented as the median and interquartile range (Me [Q25–Q75]) and compared using the Kruskal-Wallis test. Categorical variables are presented as counts and percentages and compared using the chi-square (χ^2) test or Fisher's exact test, as appropriate.

Kaplan-Meier survival curves estimated the probability of AVF thrombosis, comparing statin users versus non-users and across dose intensity groups (non-users, moderate-intensity, high-intensity). Differences in survival distributions were assessed using the log-rank test, with pairwise comparisons adjusted for multiple testing (Bonferroni). Patients who died were censored at the time of death in the Kaplan-Meier analysis. To account for death as a competing risk, Fine and Gray subdistribution hazard models were employed, defining outcomes as thrombosis, death without thrombosis, or censored. Results are reported as subdistribution hazard ratios (sHR) with 95% confidence intervals (CI). Models were adjusted for age, diabetes, and variables differing between dose groups in descriptive analyses. A p-value < 0.05 was considered statistically significant.

Results. Baseline characteristics. A total of 680 patients receiving maintenance HD were initially screened for eligibility. After applying inclusion and exclusion criteria, 562 patients were included in the final analysis. The selection process is detailed in Fig. 1.

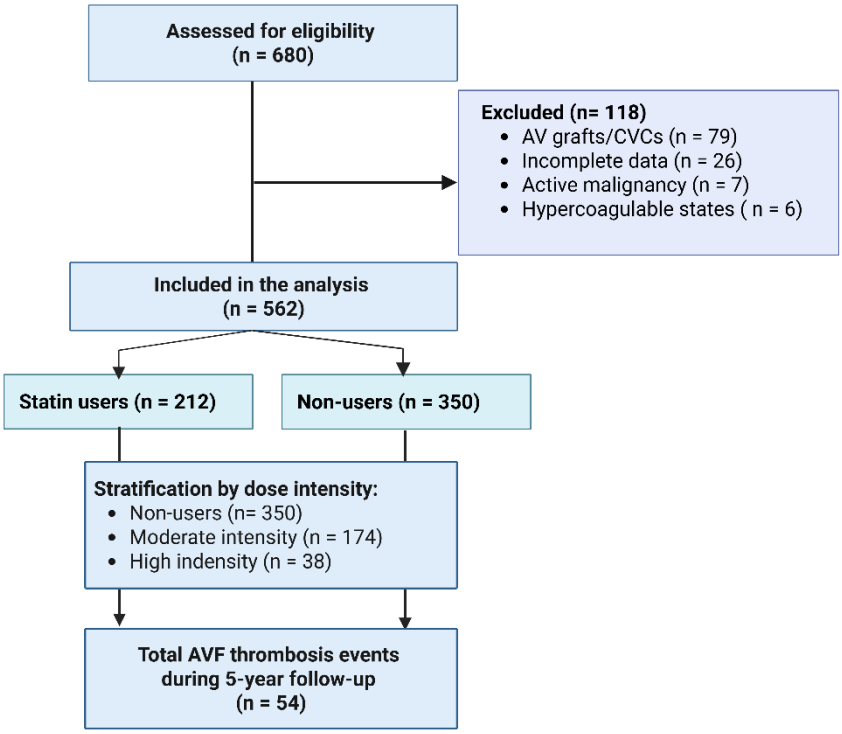

Fig. 1. The study flowchart.

Abbreviations: AVF, arteriovenous fistula, CVC, central venous catheter; HD, hemodialysis.

Of the 562 HD patients included, 212 (37.7%) were statin users and 306 (54.4%) were non-users at baseline or during follow-up. The median follow-up duration was 59 (47-60) months. Baseline demographic, clinical, and laboratory patients' characteristics stratified by lipid-lowering therapy are summarized in Table 2.

Table 2

Baseline characteristics of the study population according to statin use

Variable	All patients (n = 562)	Statin users (n = 212)	Non-users (n = 350)	p-value
Demographics				
Age, years	59 (60-66.2)	56.5 (48.4-66)	59 (50-67)	0.29
Male sex, n (%)	305 (54.3%)	104 (49.1%)	201 (57.4%)	0.06
Smoking status, n (%)	101 (17.9%)	33 (15.5%)	63 (18.0%)	0.16
Alcohol use, n (%)	49 (8.7%)	19 (8.9%)	30 (8.6%)	0.87
Clinical characteristics				
Diabetes, n (%)	109 (19,4%)	49 (23.1%)	60 (17.4%)	0.09
SBP (mmHg)	137 (130-150)	135 (130-150)	138 (132-150)	0.89
DBP (mmHg)	80 (80-90)	80 (80-90)	81 (78-90)	0.25
Pre-HD CVD history, n (%)	120 (21.3%)	18 (8.5%)	102 (29.1%)	<0.0001
CVD-related hospitalization, n (%)	99 (17.6%)	31 (14.6%)	68 (19.4%)	0.14
Non-CVD related hospitalization, n (%)	208 (37.0%)	82 (38.7%)	126 (36.0%)	0.68
Dialysis vintage (months)	47 (19.0-96.0)	53.5 (23.0-120.0)	43.0 (16.0-86.7)	0.002
Body mass index (BMI), kg/m	25.1 ± 5.1	24.8 ± 5.1	25.3 ± 5.4	0.28
Blood flow rate (mL/min)	291.2 ± 22.4	293.9 ± 24.7	289.6 ± 22.7	0.03
spKt/V	1.30 (1.2-1.43)	1.31 (1.2-1.46)	1.28 (1.13-1.42)	0.009

Continuation of Table 1

Variable	All patients (n = 562)	Statin users (n = 212)	Non-users (n = 350)	*p*-value
Total volume UF (mL)	1950 (400-2500)	2000 (350-2600)	1800 (400-2500)	0.27
Laboratory values				
Hemoglobin (g/dL)	101 (92-110.5)	103 (94-114)	100 (92-108)	0.01
CRP (mg/L)	5.39 (3.63-17.50)	6.49 (2.41-18.89)	5.24 (3.80-11.61)	0.57
Glucose (mmol/L)	5.20 (4.61-6.12)	5.06 (4.37-5.71)	5.34 (4.70-6.41)	0.008
Albumin (g/L)	39.6 (37.0-42.0)	39.7 (39.0-42.4)	39.0 (36.8-42.0)	0.15
Ferritin (ng/mL)	235 (84.5-545)	227.0 (78.2-550)	240.0 (86.1-542.0)	0.89
Calcium (mmol/L)	2.30 (2.19-2.42)	2.33 (2.23-2.46)	2.29 (2.17-2.41)	0.007
Phosphate (mmol/L)	1.62 (1.33-2.01)	1.67 (1.32-2.0)	1.60 (1.25-2.02)	0.32
iPTH (pg/mL)	320.7 (153.3-608.6)	314.9 (161.2-659.7)	331.6 (150.1-596.0)	0.53
Medications				
Erythropoiesis-stimulating agents, n (%)	548 (97.5%)	206 (97.2%)	342 (97.7%)	0.17
Iron therapy, n (%)	330 (58.7%)	125 (58.9%)	205 (58.6%)	0.73
Antihypertensives, n (%)	448 (79.7%)	174 (82.1%)	274 (78.3%)	0.28
ACEIs or ARBs, n (%)	260 (46.3%)	99 (46.7%)	181 (46.0%)	0.87
Calcium channel blockers, n (%)	245 (43.6%)	96 (45.3%)	149 (42.6%)	0.53
Beta-blockers, n (%)	197 (35.1%)	67 (31.6%)	130 (37.1%)	0.18
Alpha-blockers, n (%)	215 (38.3%)	87 (41.1%)	128 (36.6%)	0.31
Calcium-based phosphate binders, n (%)	221 (39.3%)	76 (35.8%)	145 (41.4%)	0.19

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HD, hemodialysis; iPTH, intact parathyroid hormone; SBP, systolic blood pressure; spKt/V, single-pool Kt/V; UF, ultrafiltration.

As shown in Table 1, there was no difference in the prevalence of diabetes mellitus between statin users and non-users in our cohort. However, statin users had a significantly lower prevalence of established CVD before HD initiation compared to non-users. They also exhibited a longer dialysis vintage, higher blood flow rate during HD sessions, higher dialysis adequacy, and higher hemoglobin and calcium levels. No significant differences were observed in other clinical markers or medication prescribing patterns between the groups.

Before HD initiation, only 62 of the 212 patients in the statin user group were taking statins, with the rest beginning treatment after HD initiation. Among statin users, rosuvastatin was the most common (56.1%), followed by atorvastatin (41.5%) and simvastatin (2.4%), with 82.1% receiving moderate-intensity doses and 17.9% high-intensity doses. At baseline, total cholesterol was lower in statin users, with no significant differences in LDL-C, HDL-C, triglycerides, or AIP. By the end of follow-up, statin users showed significantly lower total cholesterol, LDL-C, triglycerides, and AIP, and higher HDL-C compared to non-users, indicating more favorable lipid profile changes over time (Table 3).

Table 3

Statin types, doses, and lipid profile dynamics in statin users and non-users

Variable	Statin users (n = 212)	Non-users (n = 350)	*p*-value
Statin use characteristics			
Atorvastatin, n (%)	88 (41.5%)		
Rosuvastatin, n (%)	119 (56.1%)		
Simvastatin, n (%)	5 (2.4%)		
Moderate-intensity dosage, n (%)	174 (82.1%)		
High-intensity dosage, n (%)	38 (17.9%)		

Continuation of Table 1

Variable	Statin users (n = 212)	Non-users (n = 350)	*p*-value
Lipid profile dynamics			
Total cholesterol (mmol/L)			
Baseline	4.67 (3.78–5.39)	4.93 (4.14–5.77)	0.009
End of follow-up	4.43 (3.9–5.08)	5.07 (4.18–5.08)	<0.0001
LDL-C (mmol/L)			
Baseline	2.85 (2.23–3.56)	2.96 (2.31–3.86)	0.32
End of follow-up	2.68 (2.19–3.20)	3.10 (2.47-3.81)	<0.0001
HDL-C (mmol/L)			
Baseline	1.16 (0.89–1.41)	1.11 (0.91–1.37)	0.45
End of Follow-Up	1.21 (1.0–1.49)	1.05 (0.88–1.29)	<0.0001
Triglycerides (mmol/L)			
Baseline	1.8 (1.4–2.3)	1.9 (1.5–2.4)	0.22
End of follow-up	1.6 (1.2–2.1)	1.9 (1.4–2.5)	0.01
Atherogenic index of plasma			
Baseline	3.12 (2.50-4.08)	3.45 (2.45-4.54)	0.23
End of follow-up	3.23 (2.44-4.08)	3.56 (2.62-5.15)	0.01

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Statin use and AVF thrombosis. During the 5-year follow-up period, a total of 54 (9.6%) HD patients experienced AVF thrombosis events with 11 events (7.1%) in the statin user group and 43 events (10.6%) in the non-user group (2 = 6.4, p = 0.006). Additionally, 88 (15.7%) patients died with 27 (12.7%) in the statin user group, and 61 (17.4%) in the non-user group (2 = 2.1, p = 0.15).

Kaplan-Meier survival analysis revealed a significantly lower primary AVF thrombosis probability in statin users compared to non-users (Fig. 2).

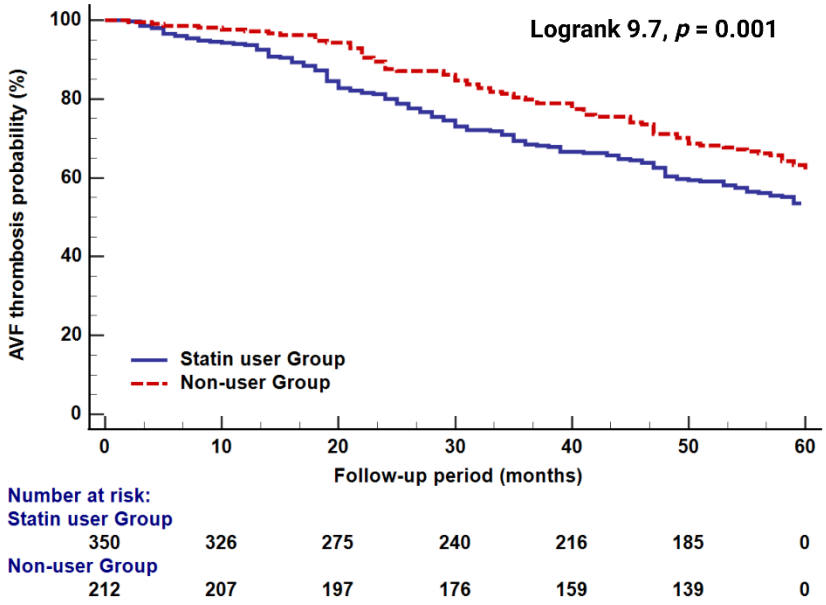

Fig. 2. Kaplan-Meier survival curves for time to AVF thrombosis in statin users vs. non-users.

Kaplan-Meier survival analysis stratified by statin dose intensity also revealed differences in AVF thrombosis-free survival (Fig. 3). Patients receiving high-intensity statins had the highest thrombosis-free survival, followed by those on moderate-intensity statins, with non-users showing the lowest survival (log-rank 10.90, p = 0.004).

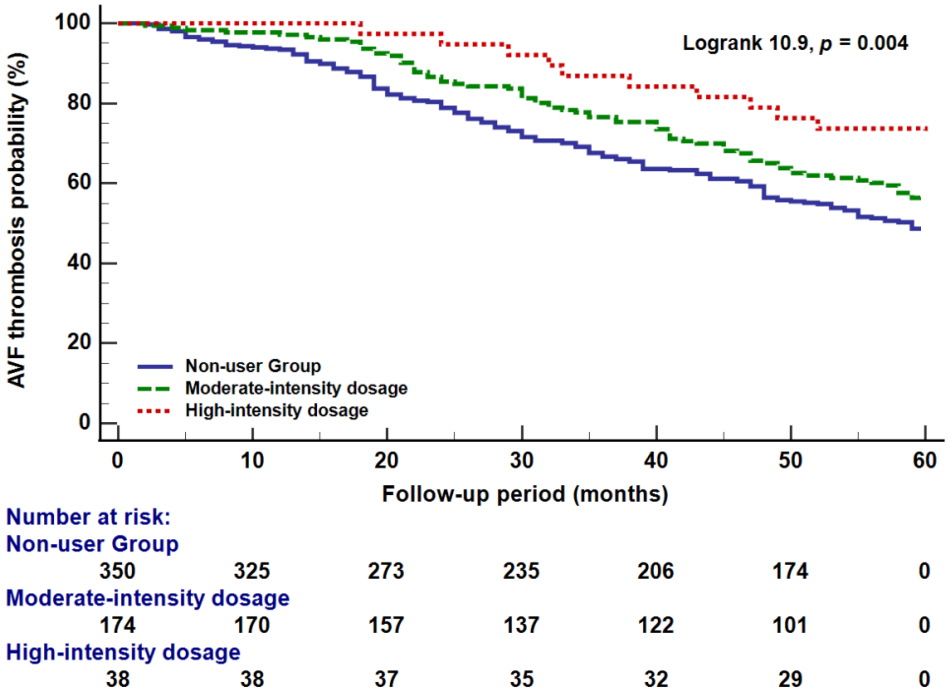

Fig. 3. Kaplan-Meier survival curves for time to primary AVF thrombosis by statin dose intensity.

Pairwise comparisons indicated lower thrombosis probabilities for moderate-intensity (p = 0.01) and high-intensity (p = 0.03) groups versus non-users, with no difference between high- and moderate-intensity (p = 0.52).

However, the Kaplan-Meier method does not account for death as a competing event, which occurred in 88 patients and may bias thrombosis risk. To address this, we employed the Fine and Gray subdistribution hazard model to estimate the effect of statin dose intensity on AVF thrombosis, accounting for competing mortality. In the Fine and Gray model, outcomes were defined as thrombosis, death without thrombosis, or censored. The unadjusted model showed a trend toward reduced thrombosis risk with increasing statin dose: moderate-intensity users had a subdistribution HR (sHR) of 0.87 (95% CI 0.72–1.18, p = 0.10), and high-intensity users had an sHR of 0.61 (95% CI 0.59–0.97, p = 0.03) compared to non-users. The overall association was significant (χ^2 = 8.01, df = 2, p = 0.018), supporting a dose-dependent effect.

Adjusting for age and diabetes, in addition to variables that differed significantly between groups in descriptive analyses (dialysis vintage, Kt/V, glucose, calcium, blood flow, and pre-HD CVD history), the Fine and Gray model did not determine statistically significant results for both moderate-intensity and high-intensity statin users compared to non-users (Table 4).

Table 4

Fine and Gray Subdistribution Hazard Models for AVF Thrombosis

Model	Exposure	HR (95% CI)	p-value
Unadjusted			
Dose Intensity	Moderate vs. Non-users	0.62 (0.30–1.08)	0.07
	High vs. Non-users	0.61 (0.59–0.97)	0.03
	Overall test	2 =8.01, df = 2	0.018
Adjusted			
Dose Intensity	Moderate vs. Non-users	0.67 (0.32–1.40)	0.16
	High vs. Non-users	0.57 (0.14–2.30)	0.26
	Overall test	2 =3.1, df = 2	0.21

Adjusted for age, diabetes, dialysis vintage, Kt/V, glucose, calcium, blood flow, and pre-HD CVD history.

HR = subdistribution hazard ratio; CI = confidence interval.

Discussion. This multicenter, retrospective cohort study evaluated the relationship between statin therapy and the risk of AVF thrombosis in patients undergoing HD, with a focus on the effect of statin dose intensity. Our findings suggest a dose-dependent protective effect, with Kaplan-Meier analysis showing a reduced probability of AVF thrombosis among statin users compared to non-users, and the lowest incidence in the high-intensity group. The unadjusted Fine and Gray model, accounting for the competing risk of death, further supported this trend, with a significant overall association driven by the high-intensity group. However, this association was attenuated after adjusting for confounders such as dialysis adequacy and pre-existing CVD, possibly due to limited events and unmeasured confounders.

The observed dose-dependent trend aligns with the biological mechanisms of statins, which extend beyond their lipid-lowering effects. Statins reduce vascular inflammation by decreasing C-reactive protein levels [19], inhibit platelet aggregation through antithrombotic pathways [7, 8], and improve endothelial function by upregulating nitric oxide production [8, 19, 20]. These mechanisms may mitigate the pro-thrombotic and inflammatory milieu often present in HD patients, where AVF thrombosis is driven by intimal hyperplasia, shear stress, and endothelial dysfunction [21, 22]. The more pronounced effect in the high-intensity group could reflect a greater suppression of these pathways, as higher doses achieve more significant reductions in inflammatory markers [19]. This suggests that the vascular benefits of statins in HD patients may be dose-dependent for maintaining AVF patency, a hypothesis that warrants further mechanistic studies.

Our findings are consistent with prior observational studies demonstrating a beneficial role of statins in AVF outcomes. Chang et al. [9] and Marinez et al. [23] reported improved AVF patency with statin use. Suh et al. specifically noted a reduction in AVF thrombosis in diabetic HD patients [24], aligning with our unadjusted results. In a recent meta-analysis, Bo-Jiang et al. found that AVF patency rates were significantly higher among statin-treated hemodialysis patients in the Asian population compared to controls [25]. Furthermore, consistent with our findings, Yamazaki et al. identified elevated LDL-C levels as an independent risk factor for reduced AVF primary patency [26]. In contrast, larger post hoc analyses [12] and a meta-analysis [10] have not demonstrated a significant association between statin use and AVF patency. This discrepancy may stem from methodological limitations in prior work, including a lack of dose stratification. When studies group all statins together without stratifying by type or dose, these specific benefits may be diluted, especially if low-intensity or less effective statins predominate in the study population [10, 23].

The clinical implications of our findings are twofold. First, the dose-dependent trend suggests that high-intensity statins could offer a targeted strategy to reduce AVF thrombosis. Clinicians might consider dose escalation in patients at high risk for AVF failure, balancing this against potential risks such as myopathy, which is more common in HD patients due to altered drug metabolism [27]. Second, the non-significant adjusted results highlight the need for personalized approaches, as the benefits of statins may vary based on patient-specific factors like dialysis adequacy or cardiovascular burden. Future studies should explore these interactions, potentially using machine learning to identify subgroups most likely to benefit from statin therapy. Moreover, larger prospective studies or RCTs are needed to confirm the dose-dependent effect, stratifying by individual statin types and doses to address the methodological limitations of prior works. Therefore, the negative or neutral findings in larger studies may reflect these methodological limitations, rather than a true absence of effect.

A key strength of our study is the use of the Fine and Gray models to account for competing risks, which is critical in HD populations with high mortality rates (15.7% in our cohort). However, our adjusted model's loss of significance underscores challenges in isolating statin effects in HD patients. This attenuation likely reflects the low number of events (54 total), reducing statistical power and widening confidence intervals. Additionally, HD patients have altered lipid metabolism [28] and a predominance of non-traditional risk factors such as chronic inflammation and oxidative stress [29], which may modify statins' effectiveness and were not fully captured in our dataset.

Several limitations must be considered when interpreting our findings. First, the retrospective design introduces potential selection bias and confounding. Although we adjusted for several variables that differed significantly between statin users and non-users, the influence of residual or unmeasured confounding cannot be completely ruled out. Second, the low number of events limited statistical power, particularly in the adjusted Fine and Gray model. Third, selection bias may have influenced the results. Patients prescribed statins may have been more likely to receive comprehensive cardiovascular care or closer monitoring, which could have contributed to better vascular access outcomes independent of statin therapy itself. Additionally, statin users had a significantly lower prevalence of pre-existing CVD in our cohort, which may reflect prescribing patterns not entirely accounted for in our adjusted models. Fourth, the majority of statin users received moderate-intensity therapy, limiting our power to detect a dose-response relationship between high-intensity statin use and AVF thrombosis risk. Moreover, simvastatin use was minimal, and no patients received combination lipid-lowering therapy, further narrowing the scope of our analysis. Finally, the study population was limited to patients from a single dialysis network in Ukraine, which may affect the generalizability of our findings to other regions or healthcare systems with different patient demographics, statin prescribing patterns, or dialysis practices. Future prospective studies and ran-

domized controlled trials are needed to validate these findings and clarify the potential role of statin therapy intensity in preserving AVF patency among patients undergoing HD.

Conclusions. Our study suggests a dose-dependent protective effect of statins against AVF thrombosis in HD patients, with high-intensity statins showing a significant unadjusted association. However, the loss of significance after adjustment and the limited number of events underscore the need for larger, prospective studies. Future research should focus on optimizing statin dosing and incorporating broader clinical variables to better understand the role of statins in improving vascular access outcomes in patients undergoing HD.

Author contributions.

Natalia Stepanova: conceptualization, methodology, formal analysis, visualization, writing - original draft;

Tetyana Ostapenko: investigation, writing - review & editing;

Valeriia Marchenko, Alina Holovanova, Mariia Lysii, Tetyana Kucher, Viacheslav Filonov, Victor Dzhur, Stetsenko Bohdan, Hanna Maroid, Nataliia Pavchak, Kateryna Rusyn, Oksana Rusyn, Bohdan Radiuk: data curation. All the authors reviewed the manuscript and approved it for publication.

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