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Patterns and predictors of statin therapy after ischemic stroke and TIA: insights from the LIPYDS multicenter study

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Abstract

Background Patients with ischemic stroke (IS) or TIA face an elevated cardiovascular risk, warranting intensive lipid-lowering therapy. Despite recommendations, adherence to guidelines is suboptimal, leading to frequent undertreatment. This study aims to evaluate the statin use after IS and TIA.

Methods LIPYDS is a multicenter, observational, retrospective study including ≥ 18-year-old patients discharged after IS/TIA from 19 Italian centers in 2021. Multivariable logistic regression analysis was used to determine (1) the association between statin prescription (Any-statin *versus* No-statin), type (High-Intensity-statin *versus* Other-statin [Moderate/Low-Intensity]) with stroke etiology (TOAST), (2) clinical variables independently associated with statin prescription in the entire cohort and within TOAST categories.

Results We included 3,740 patients (median age 75 [IQR 64–82]; median LDL-C 104 [IQR 79–131]). At discharge, 1,971 (52.7%) received a High-intensity-statin, 800 (21.4%) Other-statin, 969 (25.9%) No-statin therapy. Among patients not on statin therapy before the event ($N = 2686$ [71.8%]), 50.1% initiated High-intensity-statin (78.2% of those with Large-Artery-Atherosclerosis, 60.8% Small-Vessel-Disease, 34.7% Cardioembolic, 47.4% Undetermined etiology); in 33% the decision to abstain from initiating statin therapy persisted. Large-Artery-Atherosclerosis showed the strongest association with Any-statin (aOR 3.07 [95%CI 2.39−3.95], $p < 0.001$) and High-intensity-statin (aOR 4.51 [95%CI 3.39−6.00], $p < 0.001$), while Cardioembolic stroke showed an inverse association (respectively, aOR 0.36 [95%CI 0.31−0.43], $p < 0.001$ and aOR 0.52 [95%CI 0.44−0.62], $p < 0.001$). Stepwise regression highlighted LDL-C and previous statin therapy as consistent predictors of statin at discharge. Older patients and women were less likely to be on a high-intensity formulation.

Conclusion Statins, especially at high-intensity, are under-prescribed after IS and TIA, with older patients, women and those with non-atherosclerotic strokes being the most affected.

Keywords Ischemic stroke · Statin · LDL-C · Lipid-lowering therapy

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Introduction

Statin therapy is associated with a decreased risk of cardiovascular disease events in the general population [1] and is effective in preventing initial and recurrent strokes [2]. Current guidelines for dyslipidemia management [3, 4], classify patients with a history of ischemic stroke (IS) or transient ischemic attack (TIA) as high-risk or very high-risk for future atherosclerotic cardiovascular disease (ASCVD) events, recommending intensive lipid-lowering therapy (LLT). According to the 2021 AHA/ASA Guidelines for the Prevention of Stroke [5], statin therapy with intensive lipid-lowering effect is recommended for patients with IS presumed to be of atherosclerotic origin and LDL cholesterol (LDL-C) > 100 mg/dL to reduce the risk of stroke recurrence. Guidelines also recommend intensive statin therapy for patients with non-atherosclerotic stroke mechanisms, based on their overall cardiovascular risk and comorbid conditions [3]. A recent metanalysis [6] revealed that more intensive LDL-C lowering statin-based therapies reduce the risk of recurrent stroke, especially in patients with evidence of atherosclerosis. Despite guidelines recommendations, patients with cerebrovascular disease are less likely to receive statins or high-intensity statin therapy compared to those with coronary artery disease (CAD) [7, 8, 9]. Previous studies indicate suboptimal adherence to guidelines in statin prescriptions by neurologists [10, 11], and despite increasing use of statins and other LLT over time [9], many stroke patients remain undertreated.

Given the limited data on patterns of statin therapy after stroke, the main purpose of this study is to clarify the behavior of vascular neurologists regarding LLT, by describing the approach to statin prescription following an acute IS or TIA in an Italian cohort. The study aims to assess the frequency, identify patterns, and determine factors influencing the prescription of Any-statin and High-intensity statin therapy across the entire population of ischemic stroke patients, and within etiological stroke subgroups.

Methods

Study design

LIPYDS (*Li*pid-lowering thera*py* and L*D*L-C levels after I*S*/TIA in Italy) is a multicenter, observational, retrospective study conducted across 19 Stroke Units in Italy (see Supplemental material). The study included consecutive patients discharged with acute IS or TIA from the participating centers from January 2021 to December 2021. Patients were informed upon admission that all their clinical data would be used for research purposes and provided written consent. This study was approved by the local Ethical Committee (Comitato Etico Milano Area 3, n. 290-20042022) and it is reported in accordance with the STROBE guidelines for observational studies.

Study population

To be eligible to participate, subjects were required to be ≥18 years of age at the time of index event (IS/TIA) and have baseline LDL-C levels measured (either directly or indirectly) upon admission. Data extracted from medical records included: baseline demographics, vascular risk factors and comorbidities (current smoking, hypertension, diabetes, dyslipidemia, obesity, atrial fibrillation [AF], chronic liver disease (CLD), chronic kidney disease [CKD] stage 4–5), presence of ASCVD (including CAD, peripheral-artery-disease [PAD], cerebral-artery-disease [CeAD]; definitions provided in Supplemental material), baseline LDL-C levels, baseline LLT. Stroke severity on admission was measured by the National Institute of Health Stroke Scale (NIHSS). Functional status was evaluated at admission and discharge by modified Rankin Scale (mRS). Stroke etiology was determined based on the TOAST classification [12] which categorizes ischemic stroke into five subtypes: (1) Large-Artery-Atherosclerosis (LAA), (2) Cardioembolism (CE), (3) Small-Vessel-Disease (SVD), (4) Other determined etiology and (5) Undetermined. Each participating center independently classified patients following comprehensive diagnostic evaluation.

Lipid-lowering therapy

The prescribed statin therapy was categorized by type and dose as follows: No-statin (no statin prescribed), Any-statin (any statin prescribed), High-intensity-statin (defined as a dose expected to reduce LDL-C by ≥50% [i.e., Atorvastatin 40-80 mg or Rosuvastatin 20-40 mg]) [4], and Other-statin (comprising non-high-intensity statins including Moderate-and-Low-intensity statins). Other LLTs such as Ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-i) were also recorded (see Supplemental material for details).

Outcomes of interest

The primary outcome of interest was the proportion of patients receiving Any-statin and High-intensity-statin therapy at discharge. The entire cohort was stratified based on statin prescription type (Any-statin vs. No-statin; High-intensity-statin vs. Other-statin), and into five key subgroups according to stroke etiology (TOAST classification).

Statistical analysis

Data are presented using descriptive statistics: categorical data as counts and proportions, while continuous data as means with SD or medians with IQR ranges, as appropriate. Differences between groups (Any-statin vs. No-statin; High-intensity-statin vs. Other-statin) were analyzed through univariate analysis ($\chi 2$ Fisher's exact test for categorical variables and Wilcoxon-Mann-Whitney tests for non-normally distributed continuous variables, as appropriate). The association between statin therapy prescription at discharge (Any-statin vs. No-statin), statin type (High-intensity-statin vs. Other-statin) with stroke etiology (TOAST), was assessed through multivariable logistic regression analyses, adjusted for pre-specified baseline variables (statin therapy at baseline). To build a predictive model identifying factors influencing the prescription of Any-statin (vs. No-statin) and High-intensity-statin (vs. Other-statin) in the entire cohort and within TOAST subgroups, binary logistic regression analysis was performed, with backward stepwise elimination approach set to simplify the model, with a significant level at $p<0.05$. The following pre-specified variables were entered into the model: age, female sex, NIHSS, hypertension, diabetes, LDL-C, current smoke, AF, CKD ≥stage 4, CLD, previous hemorrhagic stroke, CAD, PAD, CeAD, any statin at baseline (for the Any-statin vs. No-statin analysis), high-intensity statin at baseline (for the High-intensity-statin vs. Other-statin analysis), mRS at discharge. Statistical analysis was performed using STATA 17 (StataCorp.2021. Stata Statistical Software: Release 17.College Station, TX: StataCorp LLC) with significant set at $p<0.05$.

Results

Patient characteristics

A total of 3,740 eligible patients (3,514 [94%] IS and 226 [6%] TIA) were enrolled. Baseline demographics and patient characteristics are shown in Table 1. Median age was 75 years (IQR 64–82). Most patients were White (97.7%), 45.7% were female. Median baseline NIHSS was 5 [IQR 2–13] and median mRS at discharge was 2 [IQR 1–4]. Hypertension was the most prevalent cardiovascular risk factor (74.7%), and AF was present in 29.9% at discharge. Median LDL-C was 104 mg/dL [IQR 79–131]). A documented history of ASCVD was noted in 1,295 (34.6%) patients (871 [23.3%] CeAD, 573 [15.3%] CAD, and 107 [2.9%] PAD). According to the TOAST classification, 661 (17.7%) patients had LAA etiology, 600 (16.0%) SVD, 1256 (33.6%) CE, 198 (5.3%) Other, and 1025 (27.4%) Undetermined. Before admission, 2,686 patients (71.8%) were not receiving statins, while 1,054 patients (28.2%) were already on statin therapy: 237 (6.3%) on High-intensity-statin and 817 (21.9%) on Other-statin therapy. Ezetimibe and/or PCSK9-i were used in 126 patients (3.4%).

Lipid-lowering therapy at discharge

Overall, 2,771 patients (74.1%) were discharged on Any-statin therapy: 1971 (52.7%) on High-intensity-statin and 800 (21.4%) on Other-statin. Nine hundred sixty-nine patients (25.9%) did not receive statin therapy (Table 1). Ezetimibe and/or PCSK9-i were prescribed for 186 patients (5.0%). There was a substantial increase in the proportion of patients receiving Any-statin therapy at discharge compared to admission, rising from 28.2 to 74.1% (Fig. 1; Table S1), primarily driven by a significant rise in patients discharged with High-intensity statin, from 6.3 to 52.7%. Ezetimibe and/or PCSK9-I prescription remained low (from 3.4 to 5.0%). Statin prescription varied by stroke etiology (Table 2): rates were highest in patients with LAA (Any-statin 87.9%; High-intensity-statin 79.0%) and SVD (Any-statin 83.3%; High-intensity-statin 61.8%). Rates were intermediate in patients with Undetermined (Any-statin 77.4%; High-intensity-statin 50.6%), and lower in patients with Cardioembolic stroke (Any-statin 62.4%; High-intensity-statin 38.5%). See Table S2 for patient characteristics by TOAST categories. Among patients not previously on statins ($N=2686$ [71.8%]), 1,345 (50.1%) initiated High-intensity-statin therapy with rates of 78.2% in LAA, 60.8% in SVD, 34.7% in CE, 47.4% in Undetermined group. Conversely, in 885 patients (33%) the decision not to initiate statin therapy persisted, with rates varying across subgroups. Patients already on High-intensity-statin tended to continue on the same therapy, while those on Other-statin often switched to high-intensity formulations (Fig. 2; Table 3).

Characteristics of any-statin and high-intensity-statin population

Baseline demographics and patient characteristics are presented in Table 1. Compared to patients discharged without statin therapy, statin users were younger (median age 74 [64–82] vs. 78 [66–85], $p<0.001$), less frequently female (42.8% vs. 54.3%, $p<0.001$), had a higher prevalence of CV risk factors and established ASCVD (39.0% vs. 22.0%, $p<0.001$). Statin users also experienced milder strokes (median NIHSS 5 [2–13] vs. 8 [3–17], $p<0.001$), resulting in better outcomes at discharge (median mRS 2 [0–3] vs. 3 [1–4], $p<0.001$). Among statin users, those on High-intensity-statin, compared to Other-statin, were younger (median age 73 [63–80] vs. 78 [66–84], $p<0.001$), and less frequently female (39.8% vs. 50.0%, $p<0.001$). While there

Table 1 Patients characteristics by statin therapy at discharge

		Statin therapy at discharge					
	Entire Cohort *N*=3740	Any Statin *N*=2771 (74.1%)	No Statin *N*=969 (25.9%)	*P* value	High-Intensity *N*=1971 (52.7%)	Other Statin *N*=800 (21.4%)	*P* value
Baseline characteristics							
Age (years), median (IQR)	75 (64–82)	74 (64–82)	78 (66–85)	<0.001	73 (63–80)	78 (66–84)	<0.001
Sex – Female	1711 (45.7)	1185 (42.8)	526 (54.3)	<0.001	785 (39.8)	400 (50.0)	<0.001
NIHSS, median (IQR)	5 (2–13)	5 (2–11)	8 (3–17)	<0.001	5 (2–10)	5 (2–12)	0.044
Baseline mRS, median (IQR)	0 (0–1)	0 (0–1)	0 (0–2)	<0.001	0 (0–1)	0 (0–1)	0.006
Previous stroke							
Ischemic stroke	485 (13.2)	370 (13.6)	115 (12.1)	0.235	259 (13.4)	111 (13.9)	0.720
Haemorrhagic stroke	32 (0.9)	19 (0.7)	13 (1.3)	0.056	12 (0.6)	7 (0.9)	0.442
ASCVD risk factors							
Hypertension	2793 (74.7)	2104 (75.9)	689 (71.1)	0.003	1480 (75.1)	624 (78.0)	0.104
Diabetes	818 (21.9)	651 (23.5)	167 (17.2)	<0.001	457 (23.2)	194 (24.2)	0.549
Dyslipidemia	2060 (55.1)	1791 (64.6)	269 (27.8)	<0.001	1281 (65.0)	510 (63.7)	0.535
Smoke (current)	725 (21.9) [3314]	599 (24.2) [2479]	126 (15.1) [835]	<0.001	468 (26.1) [1790]	131 (19.0) [689]	<0.001
Obesity	496 (18) [2763]	380 (18.8) [2025]	116 (15.7) [738]	0.065	261 (19.2) [1361]	119 (17.9) [664]	0.497
Medical comorbidities							
Atrial fibrillation	1119 (29.9)	698 (25.2)	421 (43.4)	<0.001	427 (21.7)	271 (33.9)	<0.001
CKD ≥ stage 4	131 (3.5)	78 (2.8)	53 (5.5)	<0.001	54 (2.7)	24 (3.0)	0.707
Chronic Liver Disease	108 (2.9)	71 (2.6)	37 (3.8)	0.044	53 (2.7)	18 (2.2)	0.507
ASCVD							
Established ASCVD	1295 (34.6)	1082 (39.0)	213 (22.0)	<0.001	882 (44.7)	200 (25.0)	<0.001
CAD	573 (15.3)	466 (16.8)	107 (11.0)	<0.001	350 (17.8)	116 (14.5)	0.038
PAD	107 (2.9)	89 (3.2)	18 (1.9)	0.030	67 (3.4)	22 (2.7)	0.380
CeAD	871 (23.3)	746 (26.9)	125 (12.9)	<0.001	647 (32.8)	99 (12.4)	<0.001
Baseline therapy							
Any statin	1054 (28.2)	970 (35.0)	84 (8.7)	<0.001	626 (31.8)	344 (43.0)	<0.001
No statin	2686 (71.8)	1801 (65.0)	885 (91.3)	<0.001	1345 (68.2)	456 (57.0)	<0.001
High-intensity statin	237 (6.3)	219 (7.9)	18 (1.9)	<0.001	203 (10.3)	16 (2.0)	<0.001
Other statin	817 (21.9)	751 (27.1)	66 (6.8)	<0.001	423 (21.5)	328 (41.0)	<0.001
Any Ezetimibe/PCSK9-i	126 (3.4)	97 (3.5)	29 (3.0)	0.451	64 (3.3)	33 (4.1)	0.255
TOAST							
Large-artery atherosclerosis	661 (17.7)	581 (21.0)	80 (8.3)	<0.001	522 (26.5)	59 (7.4)	<0.001
Small-vessel disease	600 (16.0)	500 (18.0)	100 (10.3)	<0.001	371 (18.8)	129 (16.1)	0.094
Cardioembolism	1256 (33.6)	784 (28.3)	472 (48.7)	<0.001	483 (24.5)	301 (37.6)	<0.001
Undetermined	1025 (27.4)	793 (28.6)	232 (23.9)	0.005	519 (26.3)	274 (34.2)	<0.001
Other	198 (5.3)	113 (4.1)	85 (8.8)	<0.001	76 (3.9)	37 (4.6)	0.354
Laboratory at baseline							
Total-C, median (IQR)	173 (145–204)	178 (147–210)	163 (139–186)	<0.001	182 (151–214)	168 (141–198)	<0.001
LDL-C, median (IQR)	104 (79–131)	108 (82–137)	95 (76–116)	<0.001	112 (84–141)	98 (76–126)	<0.001
HDL-C, median (IQR)	46 (38–56)	46 (38–56)	47 (38–56)	0.697	46 (38–55)	47 (40–56)	0.001
Triglycerides, median (IQR)	102 (78–136)	107 (81–142)	93 (72–121)	<0.001	109 (83–145)	99 (77–132)	<0.001
Outcome							
mRS discharge, median (IQR)	2 (1–4)	2 (0–3)	3 (1–4)	<0.001	2 (0–3)	2 (0–3)	0.229

ASCVD atherosclerotic cardiovascular disease; CAD coronary artery disease; CeAD cerebral artery disease; CKD chronic kidney disease; mRS modified Rankin Scale; PAD peripheral artery disease

[] *n* available data

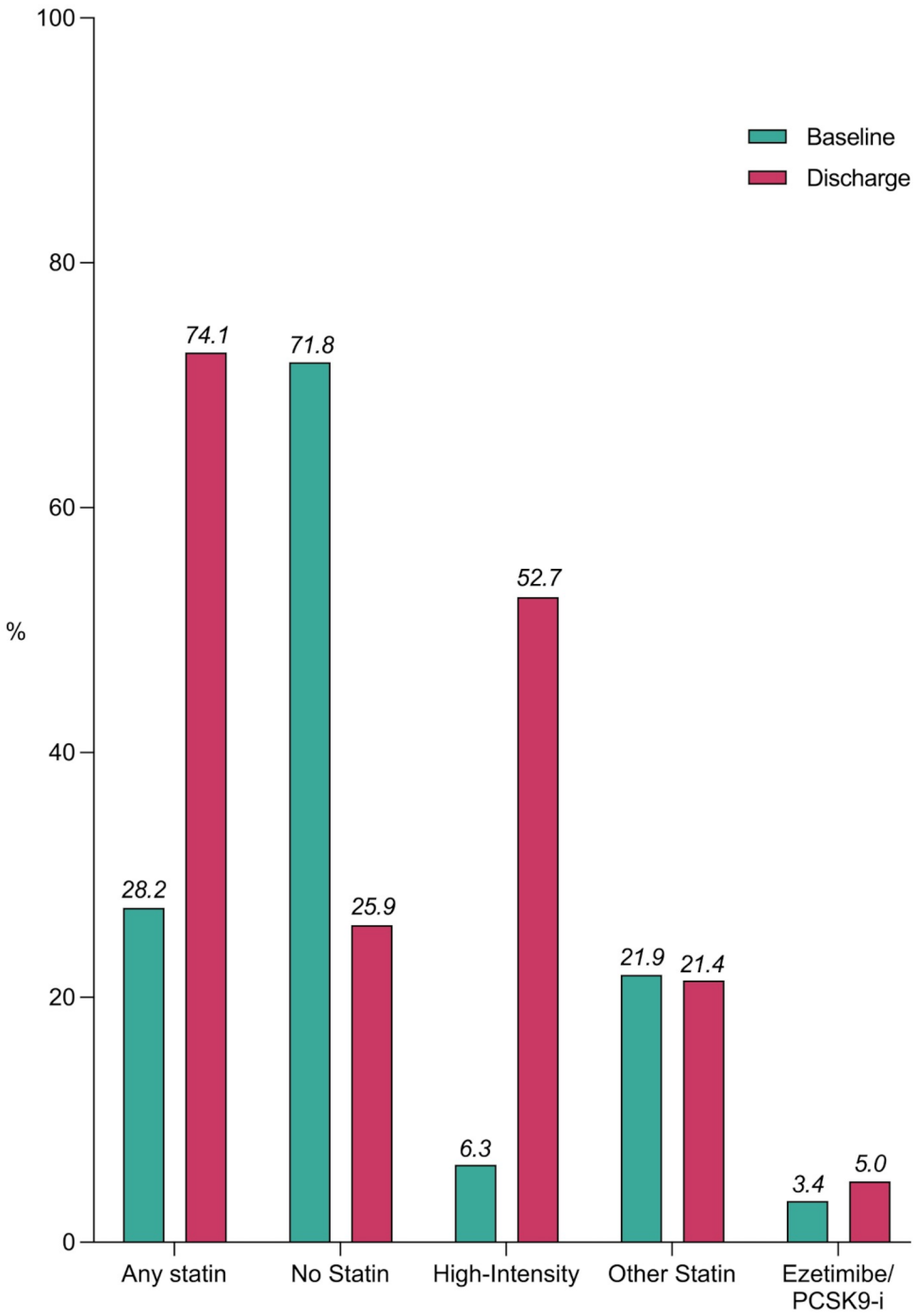

Fig. 1 Changes in Lipid-Lowering Therapy after admission

Table 2 Lipid-lowering therapy at discharge by etiology (TOAST)

	Large-artery atherosclerosis *N* = 661 (17.7%)	Small-vessel disease *N* = 600 (16.0%)	Cardioembolic *N* = 1256 (33.6%)	Undetermined *N* = 1025 (27.4%)	Other *N* = 198 (5.3%)
Lipid-lowering Therapy					
Any Statin	581 (87.9)	500 (83.3)	784 (62.4)	793 (77.4)	113 (57.1)
No Statin	80 (12.1)	100 (16.7)	472 (37.6)	232 (22.6)	85 (42.9)
High-Intensity Statin	522 (79.0)	371 (61.8)	483 (38.5)	519 (50.6)	76 (38.4)
Other Statin	59 (8.9)	120 (21.5)	301 (24.0)	274 (26.7)	37 (18.7)
Any Ezetimibe/PCSK9-i	45 (7.0)	45 (7.8)	50 (4.0)	38 (3.7)	8 (4.0)

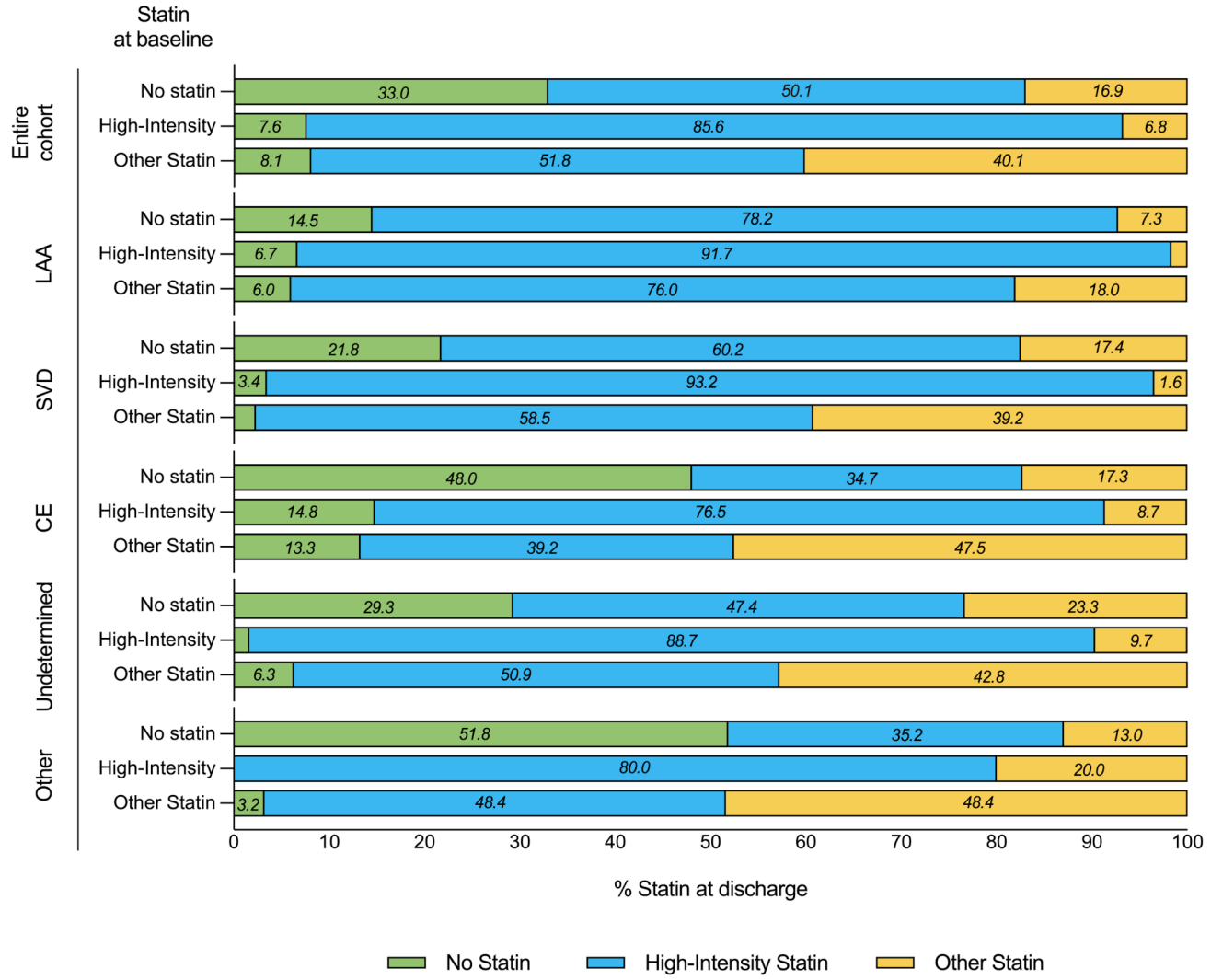

Fig. 2 Statin therapy at discharge in the entire cohort and according to TOAST classification, stratified by statin therapy at baseline

Table 3 Logistic regression analysis to evaluate the association between Stroke etiology (TOAST) and statin therapy at discharge

	Any Statin vs. No Statin		High-Intensity Statin vs. Other Statin	
	aOR (95%CI)*	*p* value	aOR (95%CI)**	*p* value
Stroke Etiology				
Large-Artery Atherosclerosis	3.07 (2.39–3.95)	<0.001	4.51 (3.39–6.00)	<0.001
Small-vessel Disease	2.04 (1.61–2.58)	<0.001	1.25 (1.00–1.56)	0.049
Cardioembolism	0.36 (0.31–0.43)	<0.001	0.52 (0.44–0.62)	<0.001
Undetermined	1.31 (1.10–1.55)	0.003	0.68 (0.57–0.82)	<0.001
Other	0.48 (0.36–0.65)	<0.001	0.86 (0.57–1.29)	0.465

*Adjusted for Any statin at baseline

**Adjusted for High-intensity statin at baseline

were no significant differences in the rates of CV risk factors between the two groups (except for current smoking), High-intensity-statin users had a higher ACSVD burden, primarily driven by a grater prevalence of CeAD (32.8% vs. 12.4%, $p<0.001$). AF was less frequent in the High-intensity-statin group (21.7% vs. 33.9%, $p<0.001$). Stroke severity, as measured by NIHSS and mRS at discharge, did not differ.

Statin therapy and TOAST classification

Adjusted multivariable logistic regression analysis, evaluating the association between statin therapy and TOAST categories, is summarized in Table 3. We found a robust association between LAA etiology and both Any-statin (aOR 3.07 [95% CI 2.39−3.95], $p<0.001$), and High-Intensity-statin (aOR 4.51 [95%CI 3.39−6.00], $p<0.001$). Conversely, CE etiology showed a significant inverse association with both Any-statin (aOR 0.36 [95%CI 0.31−0.43], $p<0.001$) and High-intensity-statin (aOR 0.52 [95%CI 0.44−0.62], $p<0.001$). Lacunar stroke exhibited a significant association with Any-statin (aOR 2.04 [95%CI 0.61−2.58], $p<0.001$), and a trend towards significance for High-intensity-statin (aOR 1.25 [95%CI 1.00−1.56], p 0.049). Patients with Undetermined etiology tended to receive a statin therapy (aOR 1.31 [95%CI 1.10−1.55], p 0.003), but were less likely to be on a high-intensity formulation (aOR 0.68 [95%CI 0.57−0.82], $p<0.001$). In case of stroke of Other etiology there was a significant inverse association with Any-statin therapy (aOR 0.48 [95%CI 0.36−0.65], $p<0.001$).

Independent predictors of any-statin and high-intensity-statin therapy

In the backward stepwise multivariable logistic regression analysis (Table 4), age (OR 1.01 [95%CI 1.01−1.02], $p=0.039$), LDL-C (OR 1.02 [95%CI 1.01−1.02], $p<0.001$), diabetes (OR 1.41 [95%CI 1.11−1.80], $p=0.005$), current smoking (OR 1.46 [95%CI 1.14−1.87], $p=0.003$), CeAD (OR 2.31 [95%CI 1.81−2.95], $p<0.001$), previous statin therapy (OR 10.10 [95%CI 7.60−13.40], $p<0.001$) were positively associated with the likelihood of receiving Any-statin therapy at discharge. Conversely, female gender (OR 0.77 [95%CI 0.64−0.93], $p=0.006$), AF (OR 0.70 [95%CI 0.57−0.85], $p=0.001$), and a higher mRS at discharge (OR 0.76 [95%CI 0.72−0.80], $p<0.001$), were negatively associated with Any-statin therapy.

Regarding High-intensity statin therapy, older age was associated with a reduced likelihood of receiving High-intensity statin (OR 0.98 [95%CI 0.98−0.99], $p=0.001$), despite its positive association with Any-statin prescription. Female gender continued to show a negative association also with High-intensity-statin use (OR 0.73 [95%CI 0.60−0.88], $p=0.001$). LDL-C (OR 1.01 [95%CI 1.01−1.01], $p<0.001$), CeAD (OR 3.42 [95%CI 2.66−4.39], $p<0.001$) and High-intensity-statin therapy at baseline (OR 8.14 [95%CI 4.53−14.64], $p<0.001$) were significant predictors of High-intensity-statin use. LDL-C at admission and previous statin therapy (both Any-statin and High-intensity-statin) were consistent independent predictors of statin therapy at discharge across all TOAST subgroups.

Discussion

Our multi-center retrospective study reveals that (1) one-fourth of patients with recent IS or TIA are discharged from a Stroke Unit without statin therapy; (2) more than two-thirds of patients discharged on statins receive a high-intensity formulation; (3) statin prescription is influenced by stroke etiology, with large-artery-atherosclerosis and cardioembolic strokes showing the highest and lowest statin prescription rates, respectively; (4) several clinical variables, including age, gender, functional outcome, LDL-C levels and pre-existing statin therapy, significantly influence statin prescription and intensity at discharge.

The relationship between statins and stroke is complex, similarly to that observed between cholesterol and stroke risk [13]. While elevated LDL-C is recognized as a risk factor for IS [14], and studies have demonstrated the benefit of statin therapy and LDL-C reduction in lowering the risk of stroke and cardiovascular events in stroke patients, this benefit is generally weaker compared to patients with CAD [15]. Most randomized studies on secondary prevention have been conducted on large populations that included a small proportion of stroke patients. These studies often combined ischemic and hemorrhagic strokes, as well as different ischemic stroke subtypes, without accounting for the pathophysiological differences between ischemia and hemorrhage or the heterogeneity in stroke etiology. To date, only two RCTs have been specifically conducted in stroke populations: (1) the SPARCL trial [16], that enrolled patients with stroke or TIA presumed to be of atherosclerotic origin (without known coronary heart disease or major cardiac sources of embolism) and demonstrated that atorvastatin 80 mg daily reduced stroke recurrence irrespective of ischemic stroke subtype; [17] (2) the TST trial [18], which showed that targeting LDL-C < 70 mg/dL was more effective than 90-to-110 mg/dL in preventing major cardiovascular events in IS/TIA patients with atherosclerosis. Based on these findings, AHA/ASA guidelines [5] advocate the use of high-intensity statins in patients with stroke caused by atherosclerosis. However dyslipidemia

Table 4 Stepwise regression analysis (and consequent selected variables) associated with any statin (vs. No-Statin) and high-intensity statin (vs. Other-Statin) at discharge, in the entire cohort and per TOAST categories

Any Statin vs. No Statin			
	Variables selected via stepwise regression analysis	OR [95%CI]*	*p* value
Entire cohort	Age	1.01 (1.01–1.02)	0.039
	Female	0.77 (0.64–0.93)	0.006
	LDL-C	1.02 (1.01–1.02)	<0.001
	Diabetes	1.41 (1.11–1.80)	0.005
	Smoke (current)	1.46 (1.14–1.87)	0.003
	AF	0.70 (0.57–0.85)	0.001
	CeAD	2.31 (1.81–2.95)	<0.001
	Chronic Liver Disease	0.57 (0.33–0.98)	0.043
	Any statin at baseline	10.10 (7.60–13.40)	<0.001
	mRS at discharge	0.76 (0.72–0.80)	<0.001
Large-Artery Atherosclerosis	LDL-C	1.01 (1.01–1.02)	0.002
	Any statin at baseline	3.62 (1.77–7.39)	<0.001
	mRS at discharge	0.63 (0.54–0.74)	<0.001
Small-Vessel Disease	LDL-C	1.03 (1.02–1.03)	<0.001
	Any statin at baseline	31.00 (9.41–108.78)	<0.001
Cardioembolism	LDL-C	1.01 (1.01–1.02)	<0.001
	Any statin at baseline	9.30 (6.36–13.57)	<0.001
	mRS at discharge	0.77 (0.71–0.83)	<0.001
Undetermined	Female	0.68 (0.47–0.98)	0.041
	LDL-C	1.02 (1.01–1.03)	<0.001
	Any statin at baseline	16.54 (8.55–31.99)	<0.001
	mRS at discharge	0.70 (0.64–0.78)	<0.001
Other	Female	0.41 (0.18–0.92)	0.031
	AF	8.03 (1.39–46.31)	0.020
	LDL-C	1.04 (1.02–1.05)	<0.001
	CAD	24.70 (2.21–272.21)	0.009
	Any statin at baseline	112.85 (12.77–997.62)	<0.001
High-Intensity Statin vs. Other Statin			
	Variables selected via stepwise regression analysis	**OR [95%CI]****	**p value**
Entire cohort	Age	0.98 (0.98–0.99)	0.001
	Female	0.73 (0.60–0.88)	0.001
	LDL-C	1.01 (1.01–1.01)	<0.001
	CeAD	3.42 (2.66–4.39)	<0.001
	High-intensity statin at baseline	8.14 (4.53–14.64)	<0.001
Large-Artery Atherosclerosis	Age	0.97 (0.94–0.99)	0.026
	LDL-C	1.01 (1.01–1.02)	0.026
	Diabetes	0.45 (0.24–0.83)	0.011
	High-intensity statin at baseline	12.45 (1.61–96.11)	0.016
Small-Vessel Disease	Age	0.97 (0.95–0.99)	0.004
	LDL-C	1.01 (1.01–1.02)	<0.001
	High-intensity statin at baseline	17.37 (2.27–133.01)	0.006
Cardioembolism	Female	0.64 (0.46–0.88)	0.006
	LDL-C	1.01 (1.01–1.02)	<0.001
	High-intensity statin at baseline	8.91 (3.46–22.93)	<0.001
Undetermined	LDL-C	1.01 (1.01–1.01)	<0.001
	High-intensity statin at baseline	6.44 (2.45–16.88)	<0.001
Other	Female	0.28 (0.11–0.72)	0.008
	LDL-C	1.02 (1.01–1.03)	<0.001

Each stepwise regression model was built including the following pre-specified baseline variables that were deemed to be associated with the prescription of statin therapy: age, female gender, baseline NIHSS, hypertension, diabetes, LDL-C, current smoke, atrial fibrillation, CKD ≥ stage 4, chronic liver disease, previous hemorrhagic stroke, CAD, PAD, CeAD, Any statin at baseline, * High-intensity statin at baseline, ** mRS at discharge

guidelines [3, 4] suggest administering statins to all stroke patients, regardless of underlying mechanism. The limited evidence in stroke population, especially in patients with non-atherosclerotic mechanisms, combined with divergent guidelines recommendations, may create uncertainty and contributes to variability in LLT approach. Furthermore, the decision between high-or moderate-intensity statin therapy is controversial, due to insufficient evidence regarding the superiority of intensive LLT [19, 20].

In our study, 74.1% of patients were prescribed statins at discharge, but only two-thirds of these (approximately half of the overall population) were on a high-intensity statins, despite guideline recommendations. Notably, one-third of patients who were not on statins before hospitalization remain untreated even after experiencing a stroke. Our finding indicate an increase in post-stroke statin use compared to previous studies [9, 10, 21], but they also confirm substantial underutilization, with many patients being undertreated [21]. Furthermore, only 5% of stroke patients were discharged with second-line LLT (Ezetimibe and/or PCSK9-i), despite evidence from the TST trial, which demonstrated that the combination of statin and ezetimibe consistently reduces the risk of recurrent strokes [22]. The underuse of LLT following stroke is particularly concerning given recent studies showing higher mortality rates and more frequent vascular events in IS/TIA patients not receiving statins [21, 23].

In line with current scientific evidence, strokes caused by LAA exhibit the strongest association with statin use, especially at high-intensity. Nevertheless, it is concerning that 12% of these patients were discharged without statin therapy. Lacunar strokes have a similar statin prescription rate (over 80%) to LAA, but despite sharing common cardiovascular risk factors, they show a weaker association with high-intensity statins. The effect of LLT in lacunar strokes remains unclear [24]. SVD involves various mechanisms such as lipohyalinosis, fibrinoid degeneration, or branch atheromatous disease, where hyperlipidemia may play a less significant role compared to hypertension or diabetes. Additionally, controversial data suggest that aggressive cholesterol reduction may increase the hemorrhagic risk, particularly in lacunar stroke [25, 26]. This concern may further reduces the inclination to use high-intensity statins in these patients. Cryptogenic strokes show a comparable overall statin prescription rate but are significantly less associated with high-intensity statin use, reflecting the heterogeneity within this population, which includes patients with both embolic and atherosclerotic mechanisms. Our findings may be partly influenced by the lower statin prescription rate (around 60%) observed in cardioembolic strokes, which account for one-third of the study population. Although observational studies suggest potential benefits of statins in reducing stroke and cardiovascular events in patients with AF [27, 28], the lack of robust scientific evidence linking cholesterol, statins, and embolic strokes, contributes to significant underuse, and cardioembolic patients remain the most undertreated. However, statins have also pleiotropic properties (antithrombotic and neuroprotective) [29] that may mediate some or all of their benefits and improve short and long-term recovery after stroke [30], but limited data are available, particularly in populations with non-atherosclerotic strokes. Among this population, recent data have shown that statin overuse in IS patients may increase the risk of potential adverse effects [31]. Therefore, until strong evidence becomes available, caution should be exercised when prescribing statins, particularly at high intensity, without a clear guideline indication.

More than 50% of the included patients were older than 75 years. Although age was a predictive factor influencing statin prescription at discharge, older patients were less likely to receive high-intensity statin therapy, with only 46% undergoing intensive treatment. At the individual level, a discrepancy may exist between the actual and perceived future risk of recurrent events in older patients, potentially leading to undertreatment. One possible explanation for this trend is the uncertainty regarding the benefit of statins in older populations, who are often underrepresented in clinical trials. Nevertheless, available evidence indicates that statin therapy effectively reduces major vascular events regardless of age [32] and current guidelines recommend high-intensity statin therapy for patients over 75 years with clinical ASCVD [3]. In our study, a poor outcome (higher mRS) at discharge was negatively associated with statin prescription. Pessimism about the prognosis may discourage neurologists from recognizing the tangible benefits of LLT in these patients.

Similarly to previous studies, our findings highlight a significant gap in LLT among women [7, 9, 23, 33], who are less likely to receive or adhere to statin therapy, particularly at high-intensity [34]. This disparity may have serious implications as statin underuse could contribute to worse outcomes in women. We hypothesize that the higher incidence of cardioembolic strokes among female patients may partly explain the less aggressive cholesterol management observed, as current guidelines [5] do not recommend statin therapy for cardioembolic stroke unless additional indications are present. Furthermore, patients with cardioembolic stroke in our study were older and had poorer outcomes at discharge. These factors, together with the known higher prevalence of advanced age and worse stroke prognosis among women, may help explain our findings. Further studies are needed to explore the underlying reasons for this disparity, especially considering the lack of evidence suggesting gender-based differences in LLT efficacy.

Baseline statin therapy and LDL-C levels are the most significant predictors of statin prescription at discharge. This underscores that elevated LDL-C strongly influence the decision to initiate any-statin or high-intensity-statin therapy, irrespective of the stroke subtype.

To our knowledge, this study represents the largest investigation conducted in high-volume stroke centers, aimed at providing insights into statin use following stroke. Recent studies [8, 35], conducted through prospective registries on patients at high or very-high cardiovascular risk, included only a small subset of individuals with cerebral ASCVD and lacked comprehensive analysis needed for meaningful conclusions about statin use after stroke. Nevertheless, our study has limitations. It is a retrospective analysis conducted exclusively in Italy, describing statin prescription patterns over a single year. In recent years, there has been growing attention to cholesterol management after stroke, potentially leading to improvements in patient care. Additionally, our analysis focused solely on discharge data. Since this was not an objective of our study, we did not assess temporal changes in statin therapy adherence or modifications after discharge, nor we did evaluate whether the prescribed LLT achieved recommended LDL-C target levels. Furthermore, we lack data on clinical follow-up and the impact of therapeutic choices on long-term outcomes, including stroke recurrence.

Despite these limitations, our study offers the most recent and detailed overview of statin use following stroke, providing valuable insights into therapeutic decisions made by vascular neurologists and the factors influencing them.

Conclusion

Our study highlights a significant underuse of statins, particularly at high-intensity, in patients discharged after IS or TIA from specialized stroke centers. This underuse may be attributed to the different stroke etiologies and uncertainties regarding the role of cholesterol and statins in non-atherosclerotic cases. Nonetheless, notable gaps in overall lipid management emerge, especially among specific groups such as older patients and women. Neurologists must prioritize lipid management in post-stroke care. Further randomized data are needed to guide treatment decisions and to evaluate the benefit of intensive statin therapies in stroke patients with non-atherosclerotic mechanisms.

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Data availability Data supporting the findings of this study and any data not published within this article are accessible in a public repository. On request, data are available from the corresponding author.

Declarations

Conflict of interest Andrea Zini received funding for speaker honoraria and consulting fees from Daiichi-Sankyo, Bayer, CSL Behring, Angels Initiative, Alexion-AstraZeneca, for scientific advisory board from Alexion-AstraZeneca and Bayer. Manuel Cappellari received consultancy or advisory board fees or speaker's honoraria from Pfizer/Bristol-Meyer-Squibb, and Daiichi-Sankyo. All other co-authors have no relevant competing interests related to this study.

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