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Statin treatment is associated with improved prognosis in patients with AF-related stroke

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ABSTRACT

Background/objectives: The most recent ACC/AHA guidelines recommend high-intensity statin therapy in ischemic stroke patients of presumably atherosclerotic origin. On the contrary, there is no specific recommendation for the use of statin in patients with non-atherosclerotic stroke, e.g. strokes related to atrial fibrillation (AF). We investigated whether statin treatment in patients with AF-related stroke is associated with improved survival and reduced risk for stroke recurrence and future cardiovascular events.

Methods: All consecutive patients registered in the Athens Stroke Registry with AF-related stroke and no history of coronary artery disease nor clinically manifest peripheral artery disease were included in the analysis and categorized in two groups depending on whether statin was prescribed at discharge. The primary outcome was overall mortality; the secondary outcomes were stroke recurrence and a composite cardiovascular endpoint comprising of recurrent stroke, myocardial infarction, aortic aneurysm rupture or sudden cardiac death during the 5-year follow-up.

Results: Among 1602 stroke patients, 404 (25.2%) with AF-related stroke were included in the analysis, of whom 102 (25.2%) were discharged on statin. On multivariate Cox-proportional-hazards model, statin treatment was independently associated with a lower mortality (hazard-ratio (HR): 0.49, 95%CI:0.26–0.92) and lower risk for the composite cardiovascular endpoint during the median 22 months follow-up (HR: 0.44, 95%CI:0.22–0.88), but not with stroke recurrence (HR: 0.47, 95%CI:0.22–1.01, *p*: 0.053).

Conclusions: In this long-term registry of patients with AF-related stroke, statin treatment was associated with improved survival and reduced risk for future cardiovascular events.

1. Introduction

The recent ACC/AHA guidelines recommend high-intensity statin therapy in patients with ischemic stroke of presumably atherosclerotic origin [1]. On the contrary, there is no specific recommendation for statin treatment in patients with non-atherosclerotic stroke, e.g. strokes related to atrial fibrillation (AF), because evidence is very scarce. AF was an exclusion criterion in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial [2]. On the other hand, patients with AF-related stroke are considered a high-risk group not only for stroke recurrence but also for future cardiovascular events and death [3–5]. Clinicians therefore remain uncertain whether to initiate statin treatment in such patients. Recently, a retrospective study in a Korean stroke registry showed that statin treatment could be associated with reduced mortality in patients with cardioembolic stroke [6].

The aim of the present study was to investigate in a non-randomized patient population whether statin treatment in patients with AF-related stroke is associated with improved survival and reduced risk for stroke recurrence and future cardiovascular events.

2. Methods

2.1. Study population and definitions

The study population was derived from the Athens Stroke Registry which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece between January 2000 and December 2011 [7]. Patients with transient ischaemic attack (TIA) or recurrent stroke are not included in the registry. Patients with AF-related stroke and no history of coronary artery disease (CAD) were included in the analysis irrespective of their baseline LDL levels. Baseline LDL levels were not an inclusion criterion because patients with cardioembolic stroke are a high-risk group for future cardiovascular events and increased cardiovascular and overall mortality [4].

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Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, current medication, time of stroke onset and hospital admission, duration of hospitalization, stroke characteristics, clinical findings and vital signs on admission, laboratory investigations and treatment. Stroke severity was assessed by means of the National Institute Health Stroke Scale score (NIHSS) at admission. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [8]. Patients were prospectively followed-up at 1, 3, and 6 months after discharge and yearly thereafter. Follow-up was routinely performed in the outpatient clinic. In case of patients with severe handicap, clinical follow-up was assessed at patient's residence or by telephone interview. The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee.

Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg diagnosed at least twice before stroke or if patient was already on antihypertensives [9]. Diabetes mellitus was defined if patient was already on antidiabetic drugs and/or insulin, or if fasting blood glucose level was >6.0 mmol/l before stroke [10]. Dyslipidemia was defined as cholesterol concentration >6.5 mmol/l the day after admission, or if patient had a previous diagnosis of dyslipidemia [11]. Coronary heart disease was assessed by questionnaire and relevant medical confirmation. Heart failure was defined according to the criteria recommended by the working group on heart failure of the European Society of Cardiology [12]. TIA was defined as complete disappearance of signs and symptoms within 24 h, regardless of infarction being shown on neuroimaging [13]. Stroke was defined according to the World Health Organization criteria [14].

A 12-lead electrocardiogram (ECG) was recorded at admission in all patients. In patients on sinus rhythm, paroxysms of AF were sought by means of repeated ECGs during hospital stay, and/or continuous ECG monitoring for several days for patients treated in the stroke unit, and/or 24-hour Holter ECG monitoring (when AF was strongly suspected from the clinical presentation and brain imaging findings). In patients with at least two episodes of AF lasting ≥30 s during such monitoring, the stroke was considered as potentially AF-related, and they were selected for the analysis. These patients were then categorized in two groups according to whether a statin was prescribed at discharge.

2.2. Outcomes and follow-up

The primary outcome of this study was overall mortality during the follow-up performed up to 5 years. The secondary outcomes were stroke recurrence and a composite cardiovascular endpoint comprising of recurrent stroke, myocardial infarction, aortic aneurysm rupture or sudden cardiac death during the follow-up up to 5 years. Death and its causes were assessed from death certificates, patients' hospital records and information from general practitioners or family physicians.

2.3. Statistical analysis

Continuous data are summarized as mean value and standard deviation (SD), and categorical data as absolute numbers and proportion. Dichotomous or categorical variables were compared with the x^2 test and continuous variables were compared with the unpaired *t*-test or Mann–Whitney *U* test. For patients lost during follow-up, survival data were censored at the last time known to be alive. Patients who experienced >1 composite vascular event during the follow-up period were censored at the time of the first event.

The Kaplan–Meier product limit method was used to estimate the probability of each outcome. Differences in Kaplan–Meier curves among the on-statin and off-statin groups were evaluated with the log-rank test. To evaluate if statin treatment is an independent predictor of outcome, univariate Cox proportional hazards analyses were initially performed for each study outcome. The covariates studied in these univariate analyses were age, sex, onset to admission time, stroke severity (assessed by the NIHSS score), TOAST mechanism, cardiovascular risk factors and comorbidities, prestroke medication, main laboratory findings at admission and basic findings on brain imaging at admission. Factors that were significant in the univariate analyses were included in the multivariate Cox model. For the univariate analysis, the level of significance was set at 10% to reduce the risk of a type II error. In the final multivariate analyses, the level of significance was set at 5%. Associations are presented as hazard ratios (HR) with their corresponding 95% confidence intervals (95% CI). Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc., version 10.0 for Windows).

Table 1
Outcome events.

	Statin treatment		
	Yes $n = 102$	No $n = 302$	*p*
Stroke recurrence	8 (7.6%)	43 (14.2%)	0.214
Myocardial infarction	1 (1%)	5 (1.7%)	1.000
Aneurysm rupture	0 (0%)	1 (0.3%)	1.000
Sudden cardiac death	2 (2%)	32 (10.6%)	0.006
Total	11 (10.8%)	81 (26.8%)	<0.001

3. Results

Among 1602 patients admitted with a first-ever ischemic stroke between January 2000 and December 2011, 1053 (65.7%) were excluded from the analysis because their stroke was not considered AF-related. Among the 549 patients with AF-related stroke, 37 (6.7%) were excluded because of in-hospital death and 108 (19.7%) patients were excluded because of history of coronary artery disease. Among the 404 patients (mean age 67.2 ± 12.3, 68.2% males) who were finally included in the analysis, a statin was prescribed at discharge in 102 (25.2%) [Supplemental figure]. The baseline characteristics of patients are summarized in the Supplemental table. 348 (86.1%) patients had a history of AF, whereas in 56 (13.9%) patients AF was newly diagnosed. There were 92 cardiovascular events in 72 patients during a median follow-up of 22 (interquartile range: 9–48) months (Table 1); there was significant difference between the two groups in the rate of sudden cardiac death (2% in the on-statin group vs. 10.6% in the off-statin group).

In the multivariate Cox proportional hazards model, statin treatment was independently associated with lower mortality (HR: 0.49, 95%CI: 0.26–0.92, Table 2) during the median 22 month follow-up. The cumulative probability of survival during the median 22 months was significantly different between the two groups: 74.0% (95%CI: 62.1–85.9%) for the on-statin group and 59.8% (95%CI: 52.2–67.4%) for the off-statin group (log-rank test 6.895, $p < 0.001$, Fig. 1).

In the multivariate Cox proportional hazard model, statin treatment was independently associated with a lower risk for the composite cardiovascular endpoint during the median 22 months follow-up (HR: 0.44, 95%CI: 0.22–0.88, Table 2). The cumulative probability was significantly different between the on-statin (17.4%, 95%CI: 6.2–28.6%) and off-statin groups (38.5%, 95%CI: 29.1–47.9%) (log-rank test 7.102, $p = 0.008$, Fig. 2).

In the multivariate Cox proportional hazard model, statin treatment was not associated with stroke recurrence during the median 22 months follow-up, despite a strong trend in favor of the on-statin group (HR: 0.47, 95%CI: 0.22–1.01, $p = 0.053$, Table 2). There was a difference of borderline statistical significance in the cumulative probability of stroke recurrence between the on-statin (14.1%, 95%CI: 3.9–24.3%) and the off-statin group (29.1%, 95%CI: 20.1–38.1%) (log-rank test 3.941, $p = 0.047$, Fig. 3).

4. Discussion

In this analysis from a large registry of consecutive patients with AF-related stroke we show that statin treatment is associated with improved survival and reduced risk for future cardiovascular events.

Current ACC/AHA guidelines recommend high-intensity statin therapy in women and men ≤75 years of age with stroke of presumably atherosclerotic origin [1]. Although there is no specific recommendation about patients with AF-related stroke, many clinicians start statin in these patients. Our finding that statin is beneficial in this high-risk group is perhaps not surprising taken into consideration that statins were shown to be beneficial also in other high-risk non-CAD groups [1]. Given the high incidence of AF-related stroke and its poor prognosis [15], this finding in an observational cohort needs to be confirmed in a randomized trial setting. Similar findings were recently reported in an analysis of a Korean stroke registry [6].

There was no significant difference between the on-statin and off-statin groups with regards to the endpoint of stroke recurrence, indicating that the beneficial effect of statins in patients with AF-related stroke was mainly driven by the reduction of cardiovascular rather than cerebrovascular events.

Pathophysiologically, our observation may be explained by various mechanisms: first, several proinflammatory biomarkers are associated with increased risk for both atrial fibrillation and myocardial infarction, and AF has been shown to generate a proinflammatory prothrombotic milieu which may in turn increase the risk for myocardial infarction

Table 2
Multivariate Cox proportional hazard analyses showing the independent predictors of 5-years a) mortality, b) stroke recurrence and c) composite cardiovascular event. Numbers represent hazard ratio and 95% confidence intervals.

	5-year mortality[a]	5-year stroke recurrence[b]	5-year composite cardiovascular event[c]
Statin at discharge	0.49 (0.26–0.92)	–	0.44 (0.22–0.88)
NIHSS score (per 1 point)	1.07 (1.04–1.10)	–	–
Age (per 10 years)	1.80 (1.40–2.30)	1.39 (1.05–1.85)	1.39 (1.09–1.79)
ACE or ACE inhibitors at discharge	0.53 (0.31–0.90)	0.52 (0.27–0.99)	–
Vitamin K antagonist	0.53 (0.34–0.81)	0.42 (0.24–0.74)	0.52 (0.32–0.84)
Diuretics	–	–	0.37 (0.16–0.85)

[a] Adjusted for smoking, cholesterol on admission, antiplatelet at discharge, diuretics at discharge and brain edema with mass effect.
[b] Adjusted for NIHSS score, smoking, ACE or ARB inhibitor at discharge, and antiplatelet at discharge.
[c] Adjusted NIHSS score, smoking, ACE or ARB inhibitor at discharge, and antiplatelet at discharge.

by promoting platelet activation, thrombin generation, and endothelial dysfunction [16–25]. The anti-inflammatory effects of statins may therefore prevent further vascular events in such patients. Second, patients with AF may suffer paroxysms of poorly controlled ventricular response, which may increase the oxygen demands of the myocardium and lead to a type 2 myocardial infarction [26]. Third, statins exert multiple pleiotropic effects which may contribute to their protective cardiovascular role such as immunomodulation, anti-inflammatory and antioxidant properties, stabilization of the atherosclerotic plaques, improved endothelial function and increased nitric oxide bioavailability both in patients with and without previous vascular events [27]. Also, statins are included among those non-arrhythmic drugs which may have a positive effect in patients with AF or in preventing AF in patients at risk [28,29]. Moreover, recent evidence shows that premorbid use of statins in AF-related stroke patients is associated with excellent collateral flow [30]. Lastly, the cause of stroke in some of our patients could have been atherosclerotic despite the presence of AF, and statin treatment could therefore have been particularly effective in such patients as they usually have atherosclerotic disease in other target organs.

Statin treatment was not significantly associated with stroke recurrence despite the presence of a strong trend ($p = 0.053$). The major pathophysiologic type of stroke recurrence in patients with an AF-related index stroke is cardioembolism, often due to inadequate anticoagulation [31]. Statins do not exert an anticoagulant effect and hence, there is no pathophysiologic basis to support an association between statins and reduction in AF-related stroke recurrence. On the other hand, statins may reduce the risk of large-artery atherosclerotic and lacunar stroke recurrences in patients with an AF-related index stroke, and may also improve the above mentioned proinflammatory prothrombotic milieu.

The main strengths of the present study include the assessment of hard clinical outcome measures such as mortality, stroke recurrence and cardiovascular events and the median follow-up period of 22 months in a consecutive series of stroke patients. Also, our analysis was not restricted only to dyslipidemic patients but included all patients irrespective of their baseline LDL levels, given that patients with AF-related stroke is a high-risk group not only for stroke recurrence but also for future cardiovascular events and cardiovascular and overall mortality [3–5].

4.1. Limitations

This study is characterized by the inherent limitations of any retrospective analysis of prospectively collected data such as collection and entry bias, and residual confounding. Moreover, other potential confounders were not assessed such as adherence to statin treatment and other secondary prevention regimens. Also, the efficiency of anticoagulation, i.e. the time within therapeutic range (TTR), for patients receiving vitamin-K antagonists was not available.

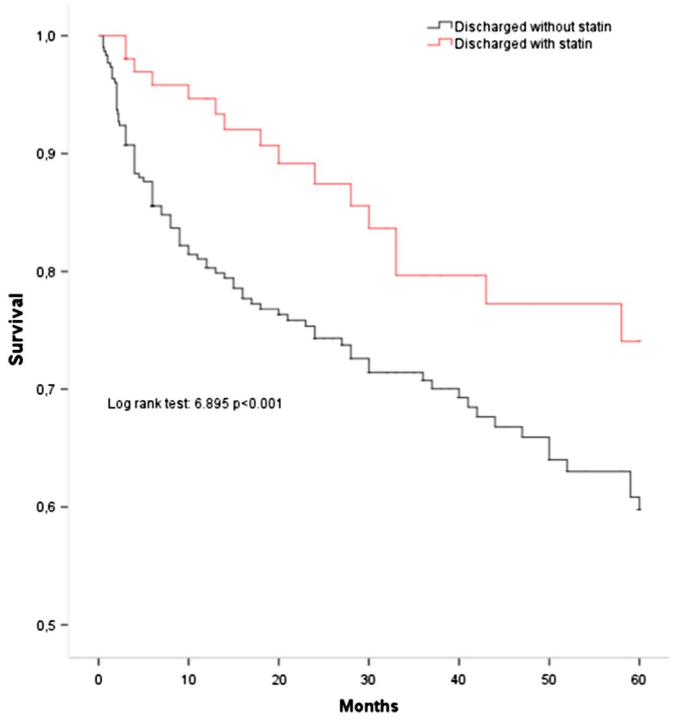

Fig. 1. Kaplan–Meier curves of the 5-years' cumulative probability of overall survival.

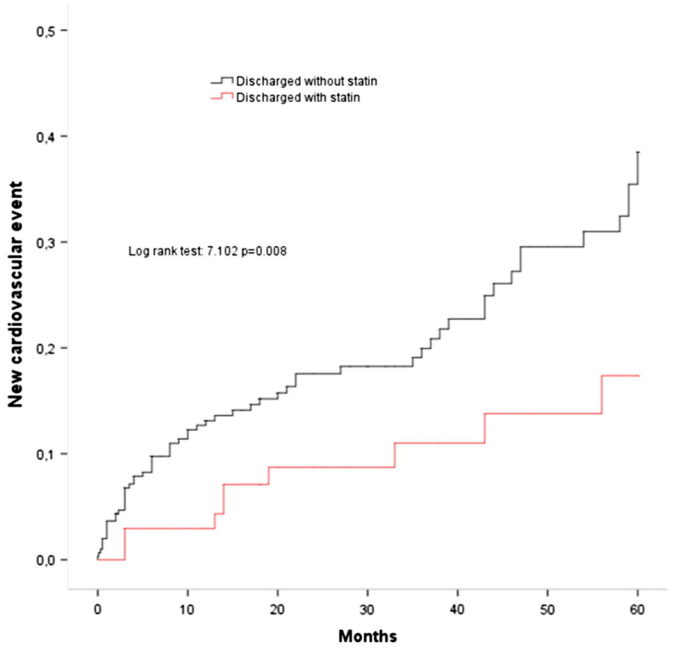

Fig. 2. Kaplan–Meier curves of the 5-years' cumulative probability of stroke recurrence.

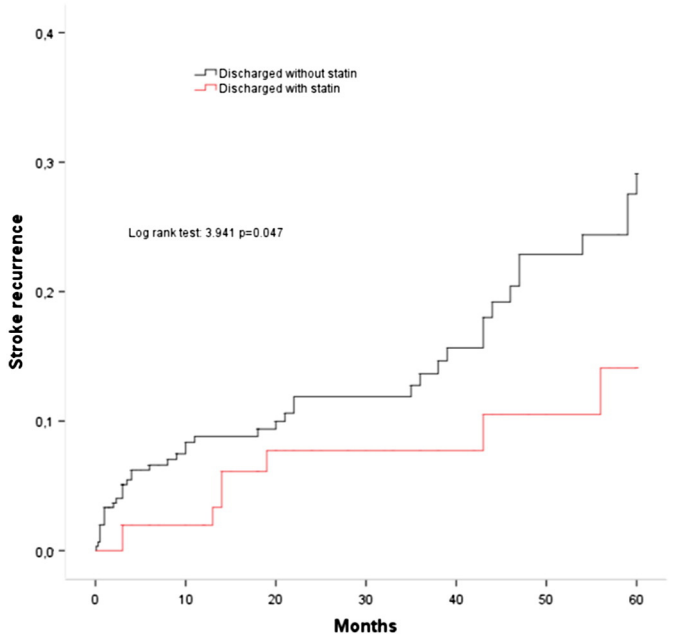

Fig. 3. Kaplan–Meier curves of the 5-years' cumulative probability of new cardiovascular event.

In conclusion, statin treatment in patients with AF-related stroke was associated with improved survival and reduced risk for future cardiovascular events in this long-term registry. Given the high incidence of AF-related stroke and its poor prognosis, further confirmation is urgently warranted in a randomized trial setting in order to substantiate a novel indication for the use of statins in clinical practice.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.09.031.

Disclosures

Dr Ntaios has received speaker fees from Boehringer Ingelheim and Sanofi; honorarium from Medtronic; and scholarships from the European Stroke Organization and the Hellenic Society of Atherosclerosis.

Dr Papavasileiou has received scholarships from the European Stroke Organization and the Hellenic Society of Atherosclerosis.

Dr Michel has received for stroke education and research through his institution (CHUV) within the last 3 years research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, and Cardiomet-CHUV; speaker fees from Bayer, Boehringer-Ingelheim, Covidien and St. Jude Medical; honoraria from scientific advisory boards from Bayer and Pfizer; consulting fees from Pierre-Fabre; and travel support from Boehringer-Ingelheim and Bayer.

Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

The other co-authors have nothing to disclose.

Author contributions

Dr. Ntaios: study concept.

Dr. Vemmos: acquisition of data.

Dr. Ntaios, Dr. Papavasileiou, Dr. Vemmos: statistical analysis and interpretation.

Dr. Ntaios, Dr. Papavasileiou: preparation of the manuscript.

Dr. Makaritsis, Dr. Lip, Dr. Milionis, Dr. Michel, Dr. Vemmos: critical revision of the manuscript for important intellectual content.

Dr. Ntaios: study supervision.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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