Review article

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Ischemic stroke in patients with atrial fibrillation – do we need to treat with statins?

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ABSTRACT

The relationship of dyslipidemia with atrial fibrillation (AF)-related stroke is not clear. The question whether patients with AF-related stroke should receive lipid lowering agents unanimously remains unanswered. Treatment with statins does not appear to be as protective as initially thought in terms of AF prevention; however, certain groups of patients may benefit from statin use. There is evidence that statins favorably affect stroke severity, in-hospital mortality, prognosis and survival of patients with AF-related stroke. Statin pretreatment is associated with better collateral circulation in patients with cardioembolic stroke. Importantly, AF frequently co-exists with several cardiovascular comorbidities, while patients with AF-related stoke may be prone to other cardiovascular events. The overall cardiovascular risk should be assessed in AF patients experiencing a stroke and treated in accordance with the proposed low density lipoprotein cholesterol (LDL-C) targets.

KEY WORDS: *Atrial fibrillation, statins, stroke*

INTRODUCTION

Ischemic stroke is associated with several underlying pathophysiologic mechanisms, including atherosclerosis of large cerebral arteries, occlusion of cerebral small vessels (lacunar strokes) and cardiac embolism, frequently in the context of atrial fibrillation (AF), while a substantial percentage of ischemic strokes has no obvious cause and are classified as embolic strokes of undetermined source (ESUS)[1].

The prevalence of AF ranges from just 0.1% in adults below 55 years to almost 10% in those over 80 years[2]. Importantly, the number of patients with AF is expected to double and the number of AF-related strokes to triple in the following decades as assessed by projections from high-income countries[2]. Of note, AF appears to be the underlying mechanism of a significant proportion of ESUS[3], and cardioembolic strokes are usually more severe compared with other ischemic stroke subtypes[4]. Therefore, prevention and treatment of AF-associated strokes is of paramount importance.

AF has strong associations with various cardiovascular (CV) comorbidities and risk factors, including arterial hypertension, cigarette smoking, heart failure, coronary heart disease (CHD), valvulopathies and diabetes mellitus (DM)[5,6]; these may contribute to its development[7] or promote both AF and atrial cardiopathy[8].

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Dyslipidemia is a well-established major risk factor for the development of cardiovascular disease (CVD), especially CHD[9,10]. The association of dyslipidemia with ischemic stroke largely depends on the etiology. When treating patients with stroke and AF, a common question rising is whether lipid-lowering treatment (LLT) would be of additive value to the prerequisite oral anticoagulation (OAC) therapy.

In this overview, we discuss the available information regarding the relationship between dyslipidemia and stroke in patients with AF, as well as the effects of LLT in this setting.

RELATIONSHIP OF LIPID PARAMETERS WITH STROKE

The relationship of lipid disorders with stroke is not consistent mainly due to the heterogeneity in the pathophysiology of different stroke subtypes. Differences in the design and populations of relative studies may also account for the incompatible findings regarding this association.

Initial meta-analyses did not show a strong positive relationship between cholesterol levels and stroke incidence[9,11]. However, many of the studies included in these meta-analyses assessed only fatal strokes, while most of these trials addressed both ischemic and hemorrhagic strokes. On the other hand, a strongly significant, positive association between serum cholesterol levels and death from non-hemorrhagic strokes was demonstrated during 6 years of follow-up in 350,977 men without CHD and DM[12]. Likewise, the INTERSTROKE study, an international case-control study in 32 countries, demonstrated that apolipoprotein (Apo)B/ApoA1 ratio is among the 10 potentially modifiable risk factors of stroke worldwide, among all ethnic groups, both genders and in all ages [odds ratio (OR) 1.84, 99% confidence interval (CI) 1.65-2.06 for highest vs lowest tertile][13]. This association was particularly true for ischemic rather than hemorrhagic strokes. Importantly, hypercholesterolemia has been recognized as a major risk factor for ischemic strokes and transient ischemic attacks (TIA) in young and middle-age stroke patients[14,15].

In a health maintenance organization-based case-control study, the highest total cholesterol quintile was associated with an increased risk of ischemic stroke compared with the lowest quintile (OR 1.6, 95% CI 1.3-2.0) with the strongest subtype associations for atherosclerotic and lacunar stroke[16]. Similarly, high low-density lipoprotein cholesterol (LDL-C) levels were associated with atherothrombotic and lacunar strokes, while this was not the case for cardioembolic strokes[17]. Still, 10% of patients with lacunar strokes have AF[18], and large-artery atherosclerosis is twice as common in patients with AF as those without[19]. These observations indicate that stroke risk in patients with AF is not entirely attributed to AF. Similarly, in a substudy of the PROFESS trial, among patients with an index stroke of cardioembolic etiology who had a recurrent stroke, the mechanism of recurrent stroke was different in half[20]. Moreover, patients with stroke and AF are prone to have not only recurrent strokes, but also other cardiovascular events like myocardial infarction and peripheral arterial disease[4].

Regarding other lipid parameters, LDL-triglycerides and angiopoietin-related protein 3 (ANGPTL3) were found to be independent predictors of ASCVD events in older adults in the Atherosclerosis Risk in Communities (ARIC) study[21]. Furthermore, several lines of evidence both from epidemiologic and genetic studies have demonstrated increased risk of incident stroke in individuals with high lipoprotein a [Lp(a)] levels[22,23]. Of note, in a recent study Lp(a) levels ≥ 100 nmol/L were associated with increased risk for recurrent stroke among patients who were either <60 years, had evident large artery atherosclerotic stroke or had *no* known AF[24]. On the other hand, high levels of high-density lipoprotein cholesterol may be protective in terms of stroke occurrence[25,26].

STATINS AND INCIDENCE OF AF

An antiarrhythmic effect of statins has been suggested as one of their pleiotropic effects[27,28]. Statins appeared as attractive candidates for upstream therapy (i.e., the use of non-antiarrhythmic drugs that modify the atrial substrate or target specific mechanisms of AF to prevent its occurrence or recurrence), mainly due to their anti-inflammatory properties, as the role of inflammation in AF is well-established. A meta-analysis of published and unpublished evidence from randomized controlled trials (RCTs) assessed the effects of statins on the incidence of AF[29]. This meta-analysis included RCTs with a minimum of 100 participants and a treatment duration of at least 6 months. Specifically, 13 short-term RCTs (N=4,414 patients, follow-up 0.02-0.42 years) and 29 longer-term RCTs (N=134,755, follow-up 1-5.2 years) were assessed. In the former, statin treatment was associated with a significant 39% decrease in AF incidence with some degree of heterogeneity (odds ratio, OR 0.61, 95% CI 0.51-0.74; 13 RCTs). On the other hand, statins did not reduce the incidence of AF compared with controls (OR 0.95, 95% CI 0.88-1.03: 22 RCTs) in the longer-term studies[29].

In contrast, in a more recent meta-analysis including 32 studies in more than 71,000 patients with sinus rhythm, statins were significantly associated with a 31% reduction in AF compared with controls (OR 0.69, 95% CI 0.57-0.83,

p<0.0001) with heterogeneous results[30]. The benefit of statin therapy was significant for the prevention of post-operative AF (homogeneous OR 0.37, 95% CI 0.28-0.51, p < 0.00001) and secondary AF prevention (OR 0.57, 95% CI 0.36-0.91, p=0.02 with significant heterogeneity). In contrast, no benefit was apparent for the prevention of new-onset AF, while the intensity of statin treatment did not appear to play a role in the risk of AF[30].

In a retrospective 2006-2015 cohort of 100,276 hypertensive individuals aged ≥ 55 without ischemic vascular disease (of whom 9,814 initiated a statin), statin use conferred on a 9% reduction in AF incidence (0.91; 0.84-0.99)[31]. The absolute risk reduction increased with higher estimated risk; however, the relative risk of AF was similar and did not reach statistical significance across risk stratification. It is likely that splitting the population into risk subgroups reduced statistical power. The 1-year number-needed-to-treat for new-onset AF was 720, which was too high to advocate the use of statins for the primary prevention of AF, even in the highest risk group. Nevertheless, this study suggested that statins may have a protective role for AF.

Finally, in contrast to the previously described meta-analysis, more recent data suggest that statins do not have a protective role against peri- and post-operative AF. Perioperative treatment with rosuvastatin did not prevent postoperative AF or perioperative myocardial damage in patients undergoing elective cardiac surgery (N=1,922) in a RCT[32]. Another study investigated whether a pause in statin therapy affects the occurrence of AF after cardiac surgery. Specifically, 301 patients without known AF already on a statin who were scheduled for elective or urgent cardiac surgery were prospectively recruited and randomized for statin re-initiation on the first (immediate statin group) or the fifth (late statin group) postoperative day, using the original medication and dosage. Early re-initiation of statins did not appear to affect the occurrence of postoperative AF in this study[33].

Overall, treatment with statins does not appear to be as protective as initially thought in terms of AF prevention. It is likely that certain groups of patients may benefit more in this setting, as demonstrated by the heterogeneity of studies included in the aforementioned meta-analyses.

Several properties of statins may account for the protection they possibly confer against AF development. Among the proposed mechanisms are regulation of nitric oxide-dependent endothelial function, reduction of inflammation and oxidative stress, prevention of high-risk plaque rupture and ischemia/reperfusion myocardial injury, as well as attenuation of atrial and ventricular remodeling. Direct mechanisms such as a statin-induced regulation of the autonomic tone and modulation of repolarization disturbances may also be involved[27].

STATIN PRE-TREATMENT IN AF PATIENTS ADMITTED WITH A STROKE

Statins appear to have favorable effects in on the severity of stroke and in-hospital mortality in patients with AF. A study which evaluated the effects of pre-stroke statin use on functional outcomes in patients with AF-related stroke demonstrated a 32% reduction in the frequency of severe strokes (OR 0.68; 95% CI 0.50-0.92; P=0.011)[34].

In a study including 1,546 AF patients taking statins in the first 90 days post-stroke and 3092 matched AF non-statin controls from the Taiwan National Health Insurance Database, the risk of recurrent stroke did not differ between the two groups during a median 2.4-year follow-up[35]. However, statin-treated AF patients had a lower risk of death during any hospitalization throughout the follow-up period (HR: 0.74, 95% CI 0.61-0.89). This reduced risk was mainly attributed to lower non-CV mortality, something which may be probably attributed to statin pleiotropic effects.

Finally, statin use appears to affect the collateral status in cardioembolic stroke. One study which investigated the effect of statins on the collateral flow of patients with cardioembolic stroke demonstrated that excellent collaterals (grade 3-4) were more frequently observed in statin users (11 patients, 50%) compared with statin-naive patients (21 patients, 27.6%; P=0.049). In multiple regression analysis, pre-stroke statin use was independently associated with excellent collaterals (odds ratio, 7.841; 95% CI 1.96–31.363; P=0.004)[36]. Importantly, the angiographic collateral grade was evaluated according to the ASITN/SIR Collateral Flow Grading System in that study.

PATIENTS WITH STROKE AND AF DISCHARGED ON STATIN

Statin treatment may be associated with improved prognosis and survival in patients with stroke and AF. Specifically, in a study including 404 patients with stroke and AF, of whom 102 (25.2%) were discharged on a statin, statin treatment was independently associated with lower mortality (HR: 0.49, 95% CI: 0.26-0.92) and lower risk of the composite CV endpoint (HR: 0.44, 95% CI: 0.22-0.88) during a median follow-up of 22 months on multivariate Cox-proportional-hazards model[37]. In contrast, the association with stroke recurrence was marginally significant (HR: 0.47, 95% CI: 0.22-1.01, P=0.053)[38].

A retrospective observational study analyzed data from 535 patients with first-ever cardioembolic stroke and classified them into non-statin, low-potency statin

and high-potency statin groups. The primary outcomes were time to mortality and time to recurrent stroke (mean follow-up 22.2 months)[39]. Statin treatment was independently associated with reduced mortality (HR 0.237; 95% CI 0.080-0.703 for non-statin vs. low-potency statin; HR 0.158; 95% CI 0.037-0.686 for non-statin versus high-potency statin). As was the case with the previous study, statin treatment did not affect the incidence of recurrent stroke[39].

Furthermore, in a study which investigated the rates and determinants of 5-year fatality, stroke recurrence, functional outcomes and prescription of secondary prevention medications in patients with AF-related stroke, statin use after the index stroke was associated with improved survival[40].

AF has been associated with the generation of a pro-inflammatory prothrombotic milieu[41,42]. Some of the pleiotropic effects attributed to statins, namely antioxidant and anti-inflammatory properties, improved endothelial function and increased nitric oxide bioavailability may account for a potent neuroprotective role associated with their use[43]. This could be a reason for the reduced mortality in statin-treated AF patients.

LIPID-LOWERING TREATMENT AND STROKE REDUCTION

Following ischemic stroke or TIA, patients are at risk not only of recurrent cerebrovascular events, but also of other major CV events. The administration of statins with or without ezetimibe reduces the risk of recurrent stroke (by 12% per mmol/L LDL-C reduction with statins), myocardial infarction and vascular death in the previously mentioned patients[44-46]. Moreover, the addition of ezetimibe to simvastatin reduced the incidence of ischemic stroke in patients stabilized after acute coronary syndrome in the IMPROVE-IT study, with the effect being larger in patients with a prior stroke[46].

The more recent drug category proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors was also shown to reduce the risk of stroke up to 25%[47-49].

In Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) icosapent ethyl significantly reduced the risk of ischemic stroke, with no excess in hemorrhagic stroke, in statin-treated patients with elevated triglycerides and atherosclerosis or DM[50]. Interestingly, an increase in the risk of AF was noticed in patients treated with eicosapentaenoic acid (EPA) in this study. Further studies with EPA assessing the effects of this agent on the occurrence of different stroke types and the incidence of AF are warranted to address the potent clinical relevance of this observation.

As already mentioned, AF frequently co-exists with several CV risk factors, including dyslipidemia. As is the case with every individual with dyslipidemia, the overall CV risk should be calculated in patients with cardioembolic stroke, and the LDL-C targets should be set accordingly (Figure 1). Most of these patients are high or very-high risk patients and should be treated with high-intensity statins. Of note, intensive vascular risk factor management after AF ablation appears to improve the underlying atrial substrate[51]. This observation also favors the use of LLT in patients with AF in terms of stroke prevention.

Of note, two recent meta-analyses favor statin use in patients with AF. In the first one post-stroke statin reduced the risk of all-cause mortality (HR 0.63; 95% CI 0.55-0.74) regardless of statin intensity, while pre-stroke statin use was associated with a lower risk of poor short-term functional outcomes (OR 0.63; 95% CI 0.47-0.85)[52]. The second one demonstrated that statin therapy was associated with a reduction in all-cause and cardiovascular mortality by 41% and 25 %, respectively in patients with AF[53].

Adherence to LLT **s**eems to be very important as is common with most long-term treatments. One study demonstrated that the relationship between statin adherence and lower risk of recurrent stroke is equally strong in patients with or without AF, suggesting that AF status should not be a reason to rule out patients from statin therapy with regard to secondary stroke prevention[54].

As these patients receive OAC we should be aware of the fact that the combination of dabigatran with simvastatin or lovastatin increases the risk of major hemorrhage compared with other statins. Thus, it may be prudent to use other statins in patients taking dabigatran or use another OAC[55].

OVERVIEW OF CURRENT GUIDELINES REGARDING LLT IN PATIENTS WITH STROKE

Current recommendations of the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) suggest that patients with a history of ischemic stroke or TIA are at very high risk of atherosclerotic CVD (ASCVD), particularly recurrent ischemic stroke, and thus, recommend intensive LDL-C lowering therapy (LDL-C <55 mg/dL and >50% reduction from baseline levels)[56]. However, there is no specific recommendation or clarification for those with AF-related stroke.

The most recent consensus of the European Stroke Organization (ESO) recommends statin administration as part of standard secondary prophylactic treatment after an ischemic stroke or a TIA. The authors suggest atorvastatin 80 mg as most benefit was observed with this scheme. They also stress the need for intensification of LLT with ezetimibe and/or PCSK9 inhibitors in order

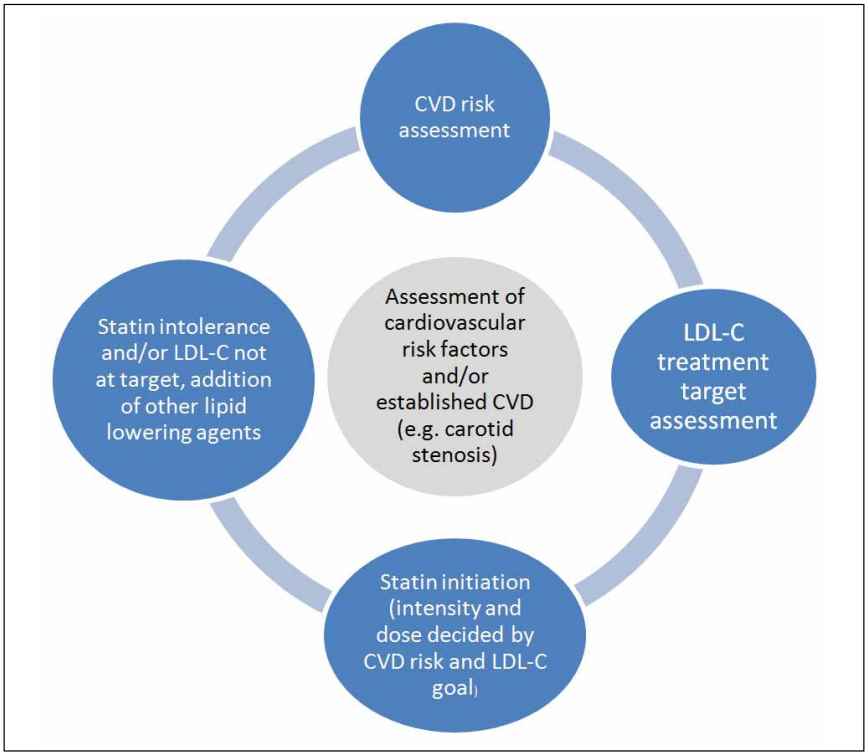

FIGURE 1. Proposed evaluation and lipid-lowering management of patients with ischemic stroke and atrial fibrillation (AF). CVD: cardiovascular disease, LDL-C: low-density lipoprotein cholesterol

to achieve LDL-C target levels. Again there is no specific recommendation for patients with AF-related stroke[57].

Similarly, the very recent guidelines of the American Heart Association/American Stroke Association (AHA/ASA) recommend the use of atorvastatin 80 mg in patients with ischemic stroke *without* CHD or major cardiac sources of embolism and LDL-C >100 mg/dL. They also stress the need for achievement of LDL-C <70 mg/dL in patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary) with the use of high-intensity statins and ezetimibe if needed (Class I, Level of evidence A) as well as in patients with multiple high-risk conditions (i.e. age ≥65 years, DM, hypertension, current smoking, history of congestive heart failure, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), estimated glomerular filtration rate (eGFR) 15-59 mL/min/1.73/m^2) with the addition of ezetimibe and/or PCSK9 inhibitors[58]. They add that if LDL-C remains >70 mg/dL, it is reasonable to treat with a PCSK9 inhibitor to prevent ASCVD events (Class 2a, Level of evidence B-non randomized).

Of note, high-risk conditions in stroke AF patients are very common. In a series of 912 consecutive acute stroke patients with documented AF, almost 77% had more than three coexistence conditions (unpublished data from The Athens Stroke Registry, personal communication).

A clinical guide by the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society also suggests that patients with ischemic stroke or TIA should receive high-intensity statin with or without ezetimibe and/or PCSK9 inhibitors in order to achieve the double treatment target of LDL-C <55 mg/dL and >50% reduction from baseline levels. The authors discuss the benefit of statins and low LDL-C levels in patients with cardioembolic stroke as shown by several studies. However, there is no specific recommendation for this patient population[59]. Overall, no organization makes a definite statement or suggestion regarding LLT in patients with AF-related stroke.

CONCLUSION

Lipid-lowering is of major importance in the secondary prevention of atherosclerotic CVD including stroke, but its role in AF incidence and AF-related stroke is not as clear. Evidence suggests that statin therapy before AF-related stroke is favorable in terms of stroke severity and in-hospital mortality from non-CV causes, whereas statin therapy upon discharge is in favor of a better short and long-term prognosis. Importantly, AF seems to be a downstream marker of vascular risk factors, such as carotid atherosclerosis or cerebral small-vessel disease, which individually produce

non-atrial stroke mechanisms. In this context, a holistic approach with intensive management of all risk factors for stroke prevention in patients with AF sounds prudent. Most of these patients appear to benefit from LLT, while adherence to treatment is advised for better outcomes. Answering the title question "do we need to treat with statins patients with ischemic stroke and AF?" the answer would be yes in almost all circumstances. Statin treatment for secondary prevention will be given to all patients with ischemic stroke and AF who have at least one major ASCVD, as well as patients who have multiple co-morbidities.

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ΠΕΡΙΛΗΨΗ

Ισχαιμικό εγκεφαλικό επεισόδιο σε ασθενείς με κολπική μαρμαρυγή – χρειάζεται να χορηγήσουμε στατίνες;

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Η σχέση της δυσλιπιδαιμίας με τα αγγειακά εγκεφαλικά επεισόδια (ΑΕΕ) που οφείλονται σε κολπική μαρμαρυγή (ΚΜ) δεν είναι ξεκάθαρη. Αντίστοιχα, το ερώτημα αν όλοι οι ασθενείς με ΑΕΕ λόγω ΚΜ πρέπει να λαμβάνουν υπολιπιδαιμική αγωγή δεν έχει απαντηθεί. Η χορήγηση στατινών δεν φαίνεται να προλαμβάνει την εμφάνιση ΚΜ. Ωστόσο, ορισμένοι ασθενείς πιθανά μπορούν να ωφεληθούν από τη θεραπεία με στατίνες. Υπάρχουν στοιχεία που υποστηρίζουν ότι οι στατίνες έχουν ευνοϊκή επίδραση στη βαρύτητα των ΑΕΕ, τη θνητότητα εντός νοσοκομείου, την πρόγνωση και την επιβίωση των ασθενών με ΑΕΕ που οφείλονται σε ΚΜ. Επιπλέον, η λήψη στατινών πριν την εμφάνιση του ΑΕΕ έχει συσχετισθεί με καλύτερη παράπλευρη κυκλοφορία σε ασθενείς με καρδιοεμβολικά εγκεφαλικά επεισόδια. Σημειώνεται ότι η ΚΜ συχνά συνυπάρχει με ποικίλους καρδιαγγειακούς παράγοντες κινδύνου, ενώ οι ασθενείς με ΑΕΕ που οφείλονται σε ΚΜ είναι επιρρεπείς στην εμφάνιση κι άλλων καρδιαγγειακών επεισοδίων. Επομένως, στους ασθενείς αυτούς πρέπει να υπολογίζεται ο καρδιαγγειακός κίνδυνος και να θεραπεύονται με γνώμονα τα επίπεδα-στόχο για την LDL χοληστερόλη.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Κολπική μαρμαρυγή, στατίνες, αγγειακό εγκεφαλικό επεισόδιο*

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