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The role of lipid-lowering treatment in the secondary prevention of ischemic stroke

Eirini Konstantinidou, Konstantinos Tziomalos

First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

Abstract

Dyslipidemia is a major risk factor for ischemic stroke. The primary goal of lipid-lowering therapy in patients with a history of ischemic stroke is low-density lipoprotein cholesterol (LDL-C) and the drug of choice for the achievement of this goal is statins. Recommended statins include atorvastatin 40-80 mg and rosuvastatin 20-40 mg. In patients who cannot achieve LDL-C targets despite treatment with these statins, addition of ezetimibe is recommended. In selected patients with LDL-C levels > 100 mg/dl despite administration of statins combined with ezetimibe, addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor should be considered. Limited data exist regarding the role of fibrates and omega-3 fatty acids in the secondary prevention of ischemic stroke.

Key words: ischemic stroke; dyslipidemia; statins; ezetimibe; PCSK9 inhibitors

Stroke is the third most common cause of death in Europe and accounts for 9% of all deaths among men and 14% of all deaths among women [1]. The lifetime risk of ischemic stroke in men and women aged 55-75 years is 14-17 and 20%, respectively [2]. Moreover, 62% of new strokes and 45% of stroke-related deaths occur in people younger than 75 years old [3]. In addition, approximately 10% of patients with ischemic stroke will die within 30 days [3]. Furthermore, stroke is a leading cause of serious long-term disability, since 60% of patients with ischemic stroke are partially dependent and 25% are completely functionally dependent for the rest of their lives [4].

The correlation between dyslipidemia and stroke has

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*Corresponding author: Konstantinos Tziomalos
First Propedeutic Department of Internal Medicine, AHEPA Hospital
1 Stilponos Kyriakidi street, Thessaloniki, 54636, Greece
Phone: +302310994621, Fax: +302310994773, E-mail: ktziomalos@yahoo.com

been shown in several epidemiological studies. In the INTERSTROKE study (13,447 patients with ischemic stroke and 13,472 controls from 32 countries) 26.8% of ischemic stroke episodes were attributed to increased apolipoprotein (apo)B/apoA1 ratio [5]. A meta-analysis of 10 prospective cohort studies (n = 238,739) reported an 11-15% decreased ischemic stroke risk per 10-mg/dl increase in high-density lipoprotein cholesterol (HDL-C) levels [6]. Another meta-analysis of 17 prospective cohort studies (n = 140,788) showed a positive association between elevated triglyceride (TG) levels and increased risk of ischemic stroke [7].

The primary goal of lipid-lowering therapy in patients with a history of ischemic stroke is low-density lipoprotein cholesterol (LDL-C)[8]. The only exception to this rule is patients with TG levels > 440-500 mg/dl, in whom TG are the primary target of lipid-lowering treatment because of the imminent risk of acute pancreatitis [8]. Lifestyle changes are an essential component of lipid-lowering treatment and include diet and exercise [8]. Diet should include a low intake of saturated fat and high intake of cereals, fruits, vegetables and fat-free dairy products [8]. Patients with a body mass index > 25 kg/m2 should also follow a hypocaloric diet [8]. In addition, > 30 min/day of moderate-intensity aerobic exercise at least 5 times a week with gradual increase of exercise duration are recommended [8].

The agent of choice for lowering LDL-C levels is statins [8]. In the Heart Protection Study (n = 3,280 patients with cerebrovascular disease and LDL-C > 135 mg/dl) treatment with simvastatin 40 mg/day for 5 years reduced the risk of major cardiovascular events by 20% compared with placebo [9]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (n = 4,731 patients who suffered a stroke or transient ischemic attack within one to six months before study entry and had LDL-C levels 100-190 mg/dl), treatment with atorvastatin 80 mg/day for 4.9 years reduced the risk for fatal or nonfatal stroke by 16% compared with placebo [10]. Moreover, treatment with atorvastatin reduced the risk for fatal stroke by 43% and the risk for coronary heart disease events (CHD) by 35% [10]. A meta-analysis of 26 randomized controlled trials (n = 169,138) showed that statins reduce the risk of ischemic stroke by 16% ($p < 0.0001$) per 39 mg/dl reduction in LDL-C levels [11]. Interestingly, a meta-analysis of 27 randomized studies (n = 113,148) showed that patients who were receiving a statin at stroke onset had 41% higher odds for a good functional outcome and 29% lower risk for death at 90 days after the event [12]. Moreover, more aggressive treatment with statins appears to be associated with better long-term functional outcome in patients discharged after an acute ischemic stroke [13].

In patients with a history of ischemic stroke, treatment with statins should be initiated immediately, in combination with lifestyle changes. The LDL-C goal is < 70 mg/dl [8]. In patients with baseline LDL-C levels between 70 and 135 mg/dl, a LDL-C reduction > 50% should also be achieved [13]. The only statins that can induce LDL-C reductions > 50% are atorvastatin 40-80 mg and rosuvastatin 20-40 mg [14]. In order to achieve LDL-C goal, statins should be administered at the maximum tolerated dose before another lipid-lowering drug is added to therapy [8].

In patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated doses of atorvastatin or rosuvastatin, addition of ezetimibe is recommended [8]. When added to statin treatment, ezetimibe reduces LDL-C levels by approximately 24% [15]. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)(n = 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had mean LDL-C levels 96 mg/dl), the combination of simvastatin and ezetimibe reduced the risk for cardiovascular events by 6.4% more than simvastatin combined with placebo [16]. Notably, the incidence of ischemic stroke was reduced by 21% [16]. However, there are no studies that evaluated the effects of ezetimibe on cardiovascular morbidity in patients with ischemic stroke.

In selected patients whose cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of atorvastatin or rosuvastatin in combination with ezetimibe, adding a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor should be considered [17]. Addition of PCSK9 inhibitor to combined statin and ezetimibe therapy induces an additional reduction in LDL-C levels by approximately 60% [18,19]. In the subgroup of patients with ischemic stroke (n = 3,366)

Table 1: **Recommendations for the management of dyslipidemia in patients with ischemic stroke**
The primary goal of lipid-lowering therapy in patients with a history of ischemic stroke is low-density lipoprotein cholesterol (LDL-C) < 70 mg/dl whereas in patients with baseline LDL-C levels between 70 and 135 mg/dl, a LDL-C reduction > 50% should also be achieved
Lifestyle changes are an essential component of lipid-lowering treatment and include hypocaloric diet (low intake of saturated fat and high intake of cereals, fruits, vegetables and fat-free dairy products) and exercise (> 30 min/day of moderate-intensity aerobic exercise at least 5 times a week)
The agent of choice for lowering LDL-C levels is statins, which should be initiated immediately, in combination with lifestyle changes
In patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated doses of atorvastatin or rosuvastatin, addition of ezetimibe is recommended
In selected patients whose cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of atorvastatin or rosuvastatin in combination with ezetimibe, adding a proprotein convertase subtilisin–kexin type 9 inhibitor should be considered
In patients who achieve LDL-C targets but have triglyceride levels > 200 mg/dl, the secondary target of lipid-lowering therapy is non-high-density lipoprotein cholesterol < 100 mg/dl, which can be achieved with lifestyle changes and/or pharmacological treatment with either fibrates or omega-3 fatty acids

included in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, patients who received evolocumab in combination with a statin experienced a 30% reduction in the incidence of cardiovascular events compared with patients who received a statin in combination with placebo [18]. Notably, even though 67% of patients achieved LDL-C levels < 40 mg/dl and 42% achieved LDL-C levels < 25 mg/dl, the incidence of adverse events did not differ between patients allocated evolocumab or placebo, except for a higher rate of injection site reactions in the former [18].

In patients who achieve LDL-C targets but have TG levels > 200 mg/dl, the secondary target of lipid-lowering therapy is non-HDL cholesterol < 100 mg/dl [8]. This target can be achieved with lifestyle changes (cessation of alcohol intake, weight loss, decreased intake of monosaccharides and disaccharides, tight glycemic control in patients with diabetes mellitus) and pharmacological treatment with either fibrates or omega-3 fatty acids [8]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (n = 5,518 patients with type 2 diabetes mellitus), the combination of fenofibrate with simvastatin did not reduce cardiovascular morbidity more than simvastatin combined with placebo [19]. However, the subgroup of patients with TG levels ≥ 204 mg/dl and HDL-C ≤ 34 mg/dl had 70% increased risk for cardiovascular events and also experienced a 31% reduction in cardiovascular events during treatment with fenofibrate [19]. Importantly, the rate of elevation in transaminase and creatine kinase levels > 3 and > 10 times the upper limit of normal was similar in patients who received simvastatin combined with fenofibrate and in those who received simvastatin combined with placebo [19]. However, the prevalence of ischemic stroke in patients included in the ACCORD trial was not reported and there are no other studies that evaluated the effects of fibrate/statin combination on cardiovascular events in patients with ischemic stroke. Regarding the effects of omega-3 fatty acids, in the Japan EPA Lipid Intervention Study (JELIS)(n = 18,615 patients with hypercholesterolemia), treatment with eisapentaenoic acid in combination with a statin reduced the incidence of CHD events by 19% compared with statin monotherapy [20]. However, the prevalence of ischemic stroke in patients included in the JELIS trial was not reported and there are no other studies that evaluated the effects of omega-3 fatty acids/statin combination on cardiovascular events in patients with ischemic stroke.

In conclusion, dyslipidemia is a major risk factor for ischemic stroke. The primary goal of lipid-lowering therapy in patients with a history of ischemic stroke is LDL-C and the drug of choice for the achievement of this goal is statins. In patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of a potent statin, addition of ezetimibe is recommended. In selected patients with LDL-C levels > 100 mg/dl despite administration of statins combined with ezetimibe, addition of a PCSK9 inhibitor should be considered. In contrast, limited data exist regarding the role of fibrates and omega-3 fatty acids in the secondary prevention of ischemic stroke.

Περίληψη

Ο ρόλος της υπολιπιδαιμικής αγωγής στη δευτερογενή πρόληψη του ισχαιμικού αγγειακού εγκεφαλικού επεισοδίου

Ειρήνη Κωνσταντινίδου, Κωνσταντίνος Τζιόμαλος

Α΄ Προπαιδευτική Παθολογική Κλινική, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

Η δυσλιπιδαιμία αποτελεί μείζονα παράγοντα κινδύνου για ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο (ΑΕΕ). Ο πρωτεύων στόχος της υπολιπιδαιμικής αγωγής σε ασθενείς με ιστορικό ισχαιμικού ΑΕΕ είναι η LDL χοληστερόλη και φάρμακο εκλογής για την επίτευξη αυτού του στόχου είναι οι στατίνες. Οι ενδεικνυόμενες στατίνες στους ασθενείς αυτούς είναι η ατορβαστατίνη 40-80 mg και η ροσουβαστατίνη 20-40 mg. Σε ασθενείς που δεν μπορούν να πετύχουν τους στόχους της LDL χοληστερόλης παρά τη χορήγηση αυτών των στατινών, θα πρέπει να προστίθεται εζετιμίμπη. Σε επιλεγμένους ασθενείς με επίπεδα LDL χοληστερόλης > 100 mg/dl παρά τη χορήγηση συνδυασμού στατίνης και εζετιμίμπης, θα μπορούσε να προστεθεί αναστολέας της PCSK9. Υπάρχουν πολύ λίγα στοιχεία για το ρόλο των φιβρατών και των ω-3 λιπαρών οξέων στη δευτερογενή πρόληψη του ισχαιμικού ΑΕΕ.

Λέξεις ευρετηρίου: ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο, δυσλιπιδαιμία, στατίνες, εζετιμίμπη, αναστολείς PCSK9

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