

UNIVERSITY OF MEDICINE AND PHARMACY OF
CRAIOVA

SUMMARY OF
DOCTORAL DISSERTATION

EFFECT OF STATIN ON ATHEROMATOUS
PLAQUE STABILIZATION IN HEMODYNAMICALLY
INSIGNIFICANT CAROTID ATHEROMATOSIS

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TABLE OF CONTENTS

INTRODUCTION	8
Chapter I: ATHEROSCLEROSIS.....	9
I.1. DEFINITION.....	9
I.2. EPIDEMIOLOGY.....	9
I.3. ATHEROMATOUS PLAQUE MORPHOLOGY AND PHYSIOPATHOLOGY	9
I.4. FACTORS INVOLVED IN ATHEROGENESIS.....	23
I.5. CLINICAL MANIFESTATIONS OF ATHEROSCLEROSIS.....	36
I.6. CLINICAL AND LABORATORY INVESTIGATION METHODS IN ATHEROSCLEROSIS.....	39
I.7. ATHEROSCLEROSIS TREATMENT.....	48
Chapter II: CAROTID ATHEROMATOSIS – RISK FACTOR FOR ISCHEMIC CEREBROVASCULAR ACCIDENT	56
II.1. ISCHEMIC CEREBROVASCULAR ACCIDENT (CVA)	56
II.2. CORRELATION BETWEEN CAROTID ATHEROMATOSIS AND THE TYPE OF CVA.....	58
II.3.ATHEROMATOUS PLAQUE MONITORIZATION - CERVICAL- CEREBRAL DOPPLER ULTRASOUND.....	58
Chapter III: STATIN PHARMACOLOGY.....	60
III.1. GENERAL CONCEPTS.....	60
III.2. STATINS – HMG CoA REDUCTASE INHIBITORS.....	60
Chapter IV: STUDY ON THE INCIDENCE OF VASCULAR RISK FACTORS IN THE PATIENTS WITH ACUTE CEREBROVASCULAR EVENTS.....	83
Chapter V: STUDY ON THE EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS.....	91
V.1. PURPOSE AND OBJECTIVES.....	91
V.2. IMPORTANCE OF THE PROBLEM APPROACHED.....	92
V.3. WORK STRATEGY.....	94
V.4. METHODS AND WORK STAGES.....	96
V.5. MEDICAL AND STATISTICAL METHODS USED IN CONDUCTING THE STUDY. EQUIPMENT USED.....	116
V.6. POSSIBLE LIMITATIONS OF THE STUDY.....	143
V.7. RESULTS EXPLOITATION.....	144
Chapter VI : RESULTS AND DISCUSSIONS.....	144
VI.1. GROUP CHARACTERIZATION.....	145
VI.2. MONITORING THE EFFECTS OF STATIN THERAPY AND OF STATIN THERAPY ADDED TO ACEI.....	181
Chapter VII: CONCLUSIONS.....	225
BIBLIOGRAPHY	230

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

Keywords: atheromatosis, statins, microemboli, inflammation, cardiovascular disease

Study on the Effect of Statin on Atheromatous Plaque Stabilization in Hemodynamically Insignificant Carotid Atheromatosis

Atherosclerosis is, nowadays, the most common cause of cardiovascular mortality and morbidity in the world, being, especially in developed countries, a major health problem. It is a multifactorial dynamic process that affects arteries throughout the body, through the formation of atheromatous plaque with lipid deposition in the vascular wall, to an extent and sequencing influenced by genetic factors, environmental factors (including risk factors) and specific medication.

The first step in the onset of atheromatosis process is the vascular endothelium damage. The local release of chemotactic factors, growth factors and mitogenic factors leads to an increased permeability of leukocyte adhesion molecules^{1,2} with the accumulation of plasma lipoproteins, of monocytes and lymphocytes and proliferation of smooth muscle cells (S.M.C.)³. The release of proinflammatory cytokines creates pathophysiological sequences that contribute to the progression of the atheromatous plaque, which shows a close connection between atherogenesis and inflammation.

Atherosclerotic lesions can increase in size, can ulcerate with the formation of thrombi on the plaque, which can trigger ischemic vascular events through hemodynamic mechanism or embolization.

Instability and complications of atheromatous plaque depend on its composition, size and location. The particularity of the vulnerable plaque is the necrotic centre where liquid cholesterol accumulates resulting in plaque rupture^{4,5}. In the ruptured atheromatous plaque⁶ cholesterol crystals form initially, triggering interleukin 1 beta (IL 1B) which causes the inflammatory response⁷ and increases the risk of acute events⁸.

The most frequent **vascular risk factors** involved in the etiology of cerebrovascular events are: high blood pressure, dyslipidemia, obesity, smoking, diabetes mellitus and inflammation.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

Studies have shown that over 19% of adults in Romania have 3 or more vascular risk factors⁹. Dyslipidemia prevalence among adult population of our country is 46%¹⁰. Through its dual valence of disease and risk factor, HBP causes vascular remodelling¹¹ in all organs (heart, kidney, brain). Diabetes history, blood glucose values and the presence of microalbuminuria¹² correlates with intima-media thickness (IMT), which is considered a marker for monitoring cardiovascular risk in patients with diabetes. Research conducted in smoking (passive and active) patients has revealed that atheromatosis is more important in those who also experienced a chronic infection¹³. Obesity is considered the public health problem of the 21st century¹⁴, an increased incidence of obesity in young people being noticed¹⁵. The increased level of proinflammatory serum markers (fibrinogen, CRP) in patients with clinically symptomatic vascular events, proves that inflammation, as a systemic phenomenon, plays a role in atherogenesis, in the increased risk of primary cardiovascular events and in the occurrence of recurrences¹⁶.

Establishing treatment formulas as effective as possible is a challenge for any practitioner. Pharmacological treatment includes several classes of drugs.

Due to their lipid-lowering, pleiotropic¹⁷ (anti-inflammatory¹⁸, antioxidant, antithrombotic, endothelial dysfunction improvement) and atheromatous plaque stabilization effects, statins are the first line therapy both in the primary¹⁹ and secondary²⁰ prevention of vascular events²¹ and in the treatment of atherosclerotic disease and its complications²².

The main effect of statins is LDL-cholesterol²³ reduction shown in patients at high risk, undergoing long-term therapy²⁴, and in particular in those having high levels of LDL-cholesterol²⁵. Statins have guidelines indication (ESC 2011)²⁶ in the treatment of dyslipidemia and in the prevention of cardiovascular disease events²⁷, the equivalent²⁸ doses for different types of statins being established according to the LDL-cholesterol reduction level. The change of the lipid profile was accompanied by a reduction by 60% of the risk of cardiac events and by 17% of the risk of CVA²⁹.

Statins are well tolerated, with rare side effects (increased transaminases³⁰, muscle damage, digestive disorders³¹, cognitive impairment, polyneuropathy³², sexual dysfunction³³, increased risk of diabetes mellitus³⁴), occurring especially after the use of high doses (40-80 mg)³⁵ and generally reversible after treatment interruption³⁶.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

The addition of angiotensin-converting-enzyme inhibitors to the treatment of the patient suffering from atherosclerosis leads to the inhibition of atherosclerosis process³⁷ with the increase of nitric oxide and the release of bradykinin. By decreasing oxidative stress they play a role in improving vascular endothelial dysfunction³⁸ with the reduction of cardiovascular event recurrence by 28% for CVA and 26% for cardiac events, effect also demonstrated in PROGRESS study³⁹.

Numerous clinical studies have demonstrated an increased risk of CVA in patients with atheromatosis and the reduction of CVA risk in patients treated with statin, by lowering the risk of major cardiovascular events⁴⁰.

Starting from the fact that in the current practice I deal with a large number of patients with cerebrovascular accidents caused by atherosclerosis, I considered necessary to summarize data from the specialized literature and to conduct a study on which the diagnosis and treatment protocol for the patients with vascular risk could be based. Thus, I chose to study the effect of statins on atheromatous plaque in the patients who have suffered an acute cerebrovascular event. The use of statins as basic medication is based on scientific arguments and justifies the choice of the research topic. By detection of microemboli, demonstrating the effect of atheromatous plaque stabilization under statin therapy acquires a distinct connotation, which is also the purpose of the scientific approach and the optimization of atheromatosis treatment is a major target.

The study aimed at reaching the following objectives:

1. Demonstrate the efficacy of statin therapy on short and medium term (3, 6, 12, 24 months) by evaluating their effect on atheromatous plaque;
2. Demonstrate the lipid-lowering and anti-inflammatory effect of statins;
3. Evaluate the tolerability and safety of statins on short and medium term;
4. Compare two groups of patients with carotid atheromatosis treated with statin, and with statin and an antihypertensive, respectively (ACEI).

The dissertation consists of two parts: the state of knowledge and personal contributions. In the first part I summarized the data existing in the specialized literature regarding the pathophysiological mechanisms of atherogenesis, the risk factors involved in the formation of atheromatous plaque, the main clinical manifestations and treatment of atheromatosis, focusing on statin therapy.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

The second part of the paper, representing a summary of the personal research, begins with a retrospective analysis of patients admitted with acute CVA over a 2-year period. The study demonstrated that the incidence of risk factors for the patients selected is similar to that of the general population in our country, involving, according to their frequency, HBP, dyslipidemia, smoking and atherosclerosis. The results of this study show an increased rate of ischemic CVA (transient or settled) in patients admitted to the department of neurology and an increased incidence of dyslipidemia (57%) and carotid atheromatosis (43%).

Formation and Characterization of the Study Group

The patients in the study group come among the patients admitted in the department of neurology and among those investigated in the specialized outpatient facility within the period 2009-2011, based on the selection criteria (patients with acute ischemic CVA and hemodynamically insignificant carotid atheromatosis).

All patients studied followed the same operational plan, were evaluated by clinical and laboratory methods (laboratory tests and EKG, ankle-brachial index measurement, echocardiography, cervical-cerebral Doppler ultrasound with microemboli detection, brain imaging). SPSS software was used for their statistic processing⁴¹.

Of the 50 patients enrolled in the study, 39 had ischemic CVA and 11 patients TIA. The patients are aged 42 to 87 years, with a prevalence of those above 60 years. The average age of the group is 68.56 ± 10.58 years. The number of men in the study is significantly higher than that of women ($p < 0.001$).

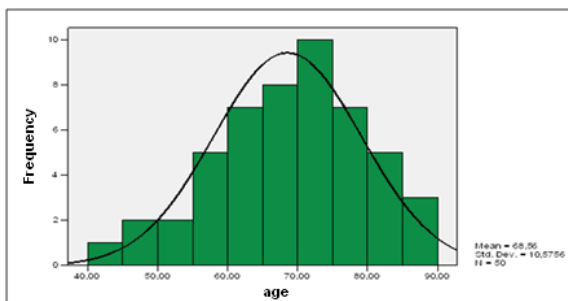


Figure 1. Patient distribution by age

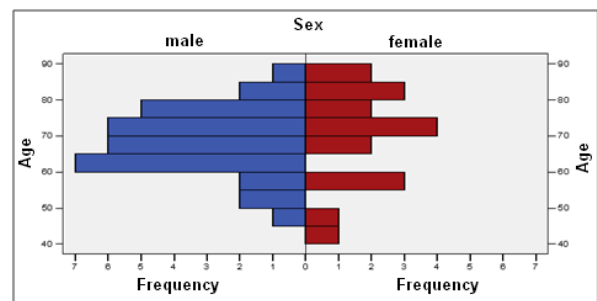


Figure 2. Group distribution by age and sex

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

At a young age (under 50 years) there are men who are prevalent, the same as in the age group 60-79 years ($p < 0.001$), while over 80 years there are women who are prevalent ($p < 0.001$). They have a life expectancy over 6 years higher than that of men and the onset of atherosclerosis is about 10 years later in women than in men.

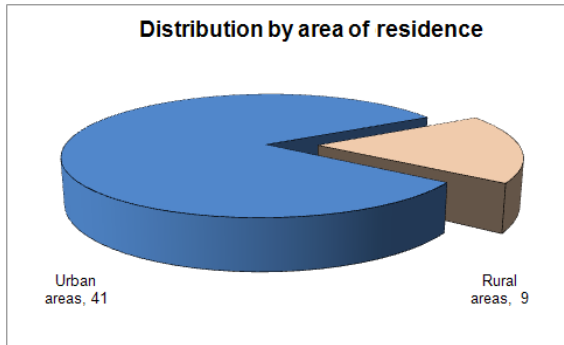


Figure 3. The group distribution by area of residence

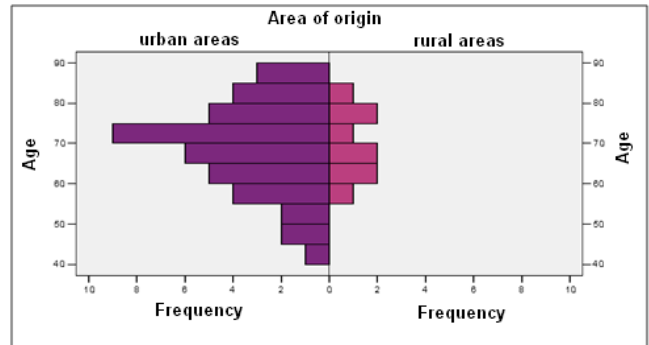


Figure 4. Patient distribution by area and age

Most patients come from urban areas, only 9 patients come from rural areas, which is due to the fact that there is an increased addressability of the patients because of the home address, and the stress and sedentary lifestyle they are exposed to contribute to the increased incidence of cardiovascular disease

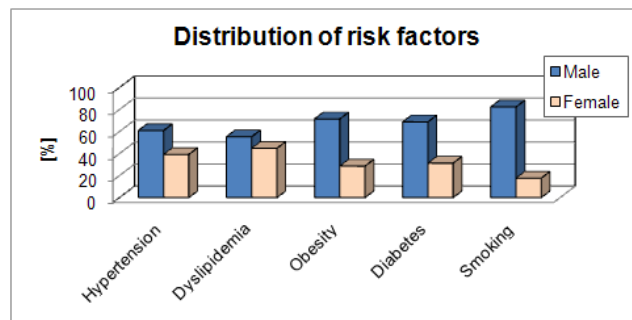


Figure 5. The distribution of risk factors for the study group.

The analysis of the incidence of risk factors shows that the most frequent were BHP (46 patients out of the 50 patients) and dyslipidemia (38 patients out of the 50 patients). Considered a risk factor but also a disease, HBP is present in 46 patients (over 90%), being more frequent in men.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

Dyslipidemia was identified in 38 patients (76%), being more common in the case of TIA, when present in all patients, as compared to the patients with CVA where it was diagnosed in 27 of 39 patients (69.2%), difference statistically significant ($p = 0.046$). Smoking (34%) is more common in men and in patients with CVA.

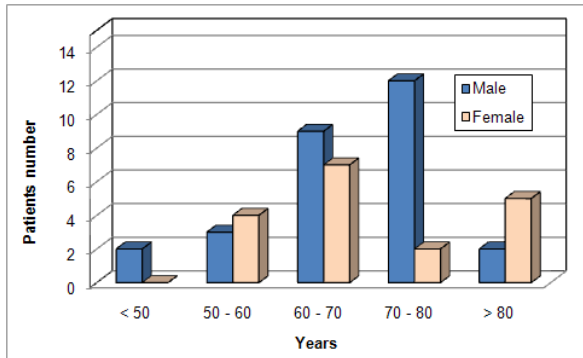


Figure 6. Distribution of patients with BHP by age and sex

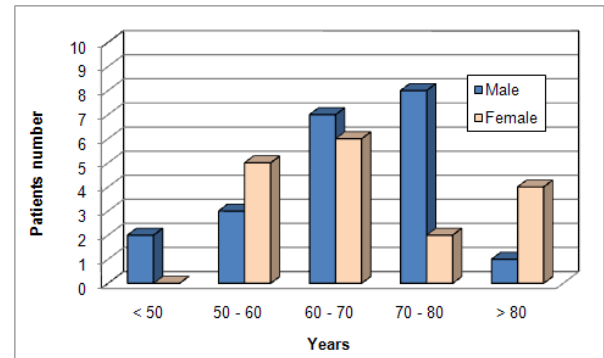


Figure 7. Distribution of patients with dyslipidemia by age and sex

In this study, obesity was found in 14 patients (28%) of the group, which gives it a lower influence on cardiovascular risk. It is more prevalent in younger women and in urban areas, but with no statistically significant correlation (residence area $p = 0.677$; sex $p = 0.505$; age $p = 0.483$). Diabetes mellitus and changed fasting glucose was present in 16 of the 50 patients (32%) and metabolic syndrome occurs in 19 of the 50 patients (38%) of which 57.9% are men, which is consistent with the specialized studies in which the metabolic syndrome is more prevalent in men.

As regards the association of vascular risk factors, most have 2 and 3 risk factors (34 patients), and 9 patients have a higher number.

Group Characterization according to Vascular Carotid Damage

The extent of damage to the carotid vessels and the influence of statin therapy were evaluated by cervical-cerebral Doppler ultrasound. Upon enrolment in the study, the appearance of atheromatous plaques and the presence of microemboli were analyzed, and the intima-media thickness (IMT) was measured, having values between 0.9 and 1.3 mm. Most of the patients from the study group had an increased IMT.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

The average IMT upon enrolment in the study was insignificantly different ($t = 1.022$, $df = 48$, $p = 0.312$) among patients with CVA ($M = 1.12$, $SD = 1.09$) and patients with TIA ($M = 1.09$, $SD = 0.09$) and was statistically significant positively correlated (Spearman's $\rho = 0.293$, $p = 0.039$) with age, presence of diabetes (Spearman's $\rho = 0.377$, $p = 0.007$) and obesity (Spearman's $\rho = 0.281$, $p = 0.048$).

The ultrasound appearance of atheroma plaques in the patients included in the group is different from type I to type III of plaque, in the following proportions: 7 patients (14%) had type I, 25 patients (50%) had type II and 18 patients (36%) had type III. The type of atheromatous plaque correlates positively with the age of the patients (Spearman's $\rho = 0.673$, $p = 0.001$). Dyslipidemia presence correlates negatively with atheromatous plaque degree (Spearman's $\rho = 0.0321$, $p = 0.023$), resulting in a lower degree of the plaque (“soft plaque”).

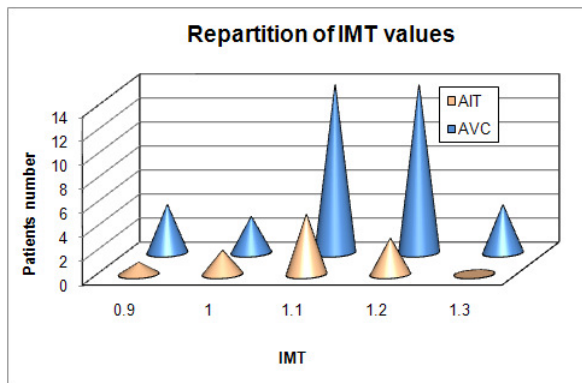


Figure 8. Distribution of patients according to vascular events and IMT

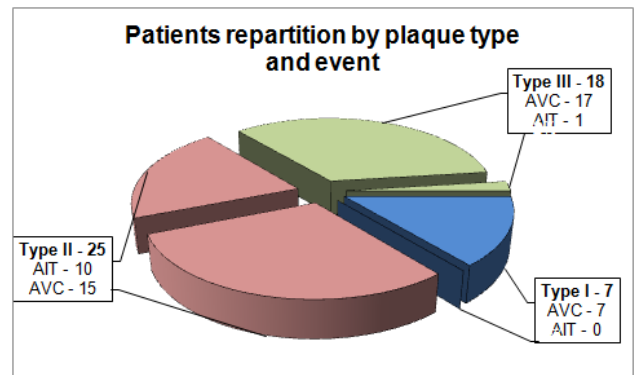


Figure 9. Distribution of patients by vascular event and atheromatous plaque

The stability of the atheromatous plaque was evaluated based on the number of microemboli. In the majority of patients between 2 and 4 microemboli were detected for 30 minutes. The average number of microemboli upon enrolment in the study did not differ statistically significant ($t = 0.862$, $df = 48$, $p = 0.393$) between the two groups: with CVA ($M = 3.12$, $SD = 1.08$) and with TIA ($M = 3.45$, $SD = 1.21$) and was not significantly correlated with the risk factors studied.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

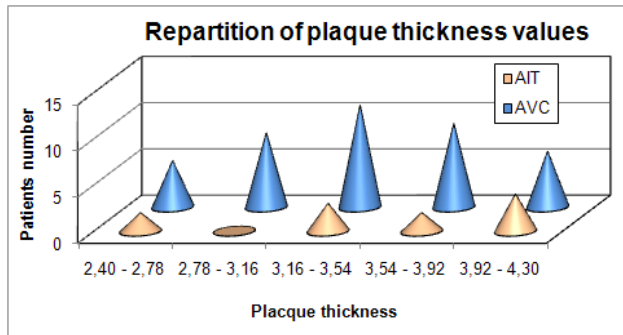


Figure 10. Patients distribution according to vascular event and the thickness of plaque

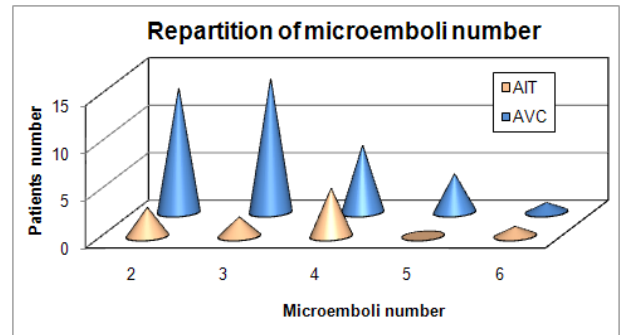


Figure 11. Patients distribution according to the event and the number of vascular microemboli

Influence of Statin Therapy on Atheromatous Plaque Stability

Statin therapy has been recommended according to the guidelines for management of dyslipidemia and to the European guidelines on cardiovascular disease prevention⁴². In the study, for an objective statistical analysis, in the conditions of similar therapeutic effects, the equivalent dose for rosuvastatin was used⁴³. It is found out that for each type of statin a slight but statistically insignificant ($p = 0.083$) decrease of the average IMT takes place starting with the 4th visit (12 months of treatment), decrease that is maintained until the end of the study (24 months). At 24 months, the decrease in the value of the IMT is statistically significant ($p < 0.001$) regardless of the type of statin given. The size of the atheroma was influenced after 12 months of treatment supported with high statin doses, a slight regression of the average size, of about 1.3%, being observed after 24 months. After 6 months of treatment the appearance of the atheromatous plaque (determined by its structure) presented minor changes.

The appearance of the atheromatous plaque significantly correlates with IMT values upon all visits (3 months $p = 0.007$; 6 months $p = 0.024$; 12 months $p = 0.043$ and 24 months $p = 0.010$). Thus, IMT decreasing is accompanied by a change in the structure of the atheromatous plaque. The type of statin does not statistically significant influence the type of plaque over the periods up to 12 months (Kruskal Wallis test - 3 months $p = 0.064$, 6 months $p = 0.056$, 12 months, $p = 0.053$), the significant difference occurs at 24 months ($p = 0.039$).

The average number of microemboli decreases by 70.63% on the short term (0-6 months) and by 95.63% on the medium term (0-24 months).

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

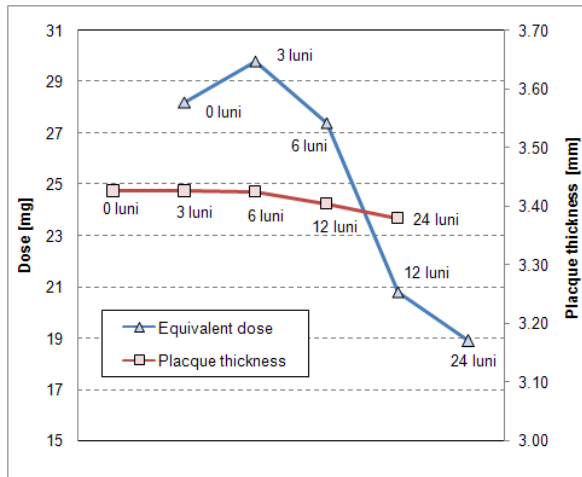


Figure 12. Evolution of the average thickness of plaque on statin therapy

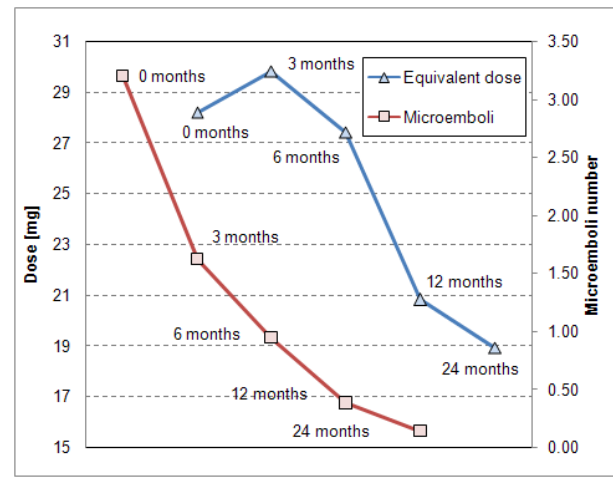


Figure 13. Evolution of the microemboli number on statin therapy.

The decrease in the number of microemboli from one visit to another is statistically significant ($p < 0.001$) but does not differ in terms of the type of statin administered ($p = 0.266$). The relationship between the number of microemboli and the equivalent dose of statin is also supported after 12 months of treatment ($p = 0.040$).

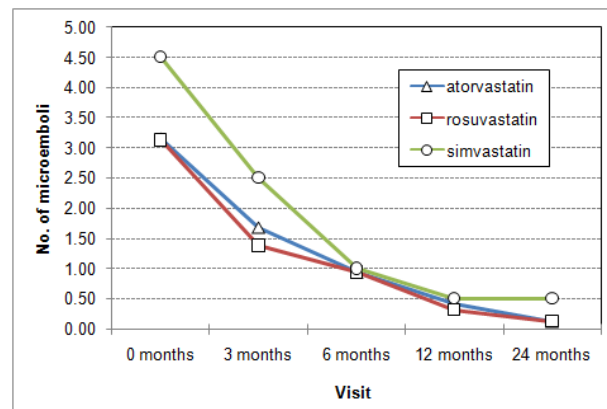


Figure 14. Evolution of the microemboli number on visits and type of statin.

Atheromatous plaque instability was correlated with vascular disease recurrences, most of them being in the first period (0-6 months), especially in the first 3 months (13 patients out of 17 patients who had a recurrence). They are more common in the patients with TIA, a significantly positive correlation existing ($\rho = 0.346$ $p = 0.014$). Under statin therapy the recurrence rate significantly decreased in the period 6 - 12

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

months of study (4 patients from the 50-patient group, representing 8%), decrease that was directly proportional to the decrease in the number of microemboli and inversely proportional to the therapeutic dose.

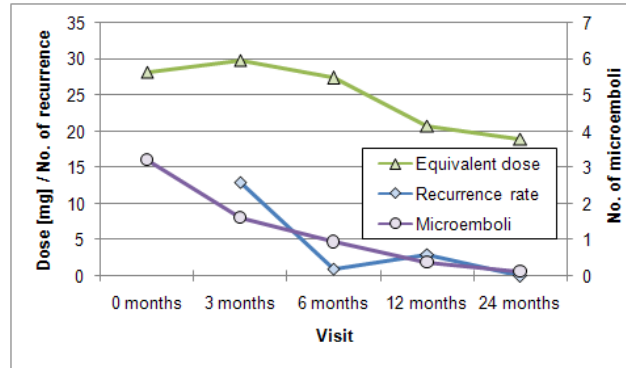


Figure 15. Variation of the microemboli number, medium dose, and the number of recurrences.

For the patients with recurrence at 3 months a significantly positive correlation with the number of microemboli during the first 12 months was noticed: V0 ($\rho = 0.310$ $p = 0.029$), V3 ($\rho = 0.283$ $p = 0.047$), V12 ($\rho = 0.287$ $p = 0.043$) which supports the hypothesis that the unstable plaque has an increased risk of vascular event and recurrence.

The patients with cerebrovascular recurrence had atheromatous plaques larger in size (3.83 mm), predominantly type II, and lower IMT (1.14 mm) compared to the patients with coronary recurrences whose plaques were type II and III with lower size (3.46 mm) and slightly higher average IMT (1.16).

More than half of the patients with recurrence had inflammatory syndrome, the statistical analysis showing a significantly positive correlation between the recurrence at 3 months and ESR ($\rho = 0.337$ $p = 0.017$), decreasing in the first months when the statin doses administered were also higher. This supports the fact that statin decreases the inflammatory syndrome, the effect being dose dependent, more accentuated in the first 6 months from the occurrence of the vascular event. Analysing the inflammatory syndrome, it is found out that it is significantly positively correlated with the number of microemboli ($p = 0.008$), with plaque thickness ($p = 0.021$) upon the initial visit but also in the first 3 months. After carrying out the multivariate analysis it was found out that it decreases statistically significant upon the 5 moments, independent of the type of statin (fibrinogen ($p < 0.001$) and ESR ($p = 0.013$)).

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

Between lipid profile and recurrence I have found out that there is a negative correlation with cholesterol ($\rho = -0.300$, $p = 0.034$) and LDL-cholesterol ($\rho = -0.021$, $p = 0.00023$). The multivariate analysis showed a significant effect of the statin dose used ($F = 7.32$, $p = 0.002$) on cholesterol and LDL-cholesterol ($F = 3.791$, $p = 0.001$). They decrease after 3-6 months of treatment with medium to large doses of statin.

The statistical analysis underlines positive correlations between metabolic syndrome (47%), peripheral artery disease ($\rho = 0.363$, $p = 0.0010$) and the risk of recurrence.

Assessing the Tolerability of Statin Therapy

Just like in other studies in which a good safety and tolerance was demonstrated in elderly patients who were given medium doses of statin (PROSPER study) in our case, as well, the therapy with moderate doses of statins was well tolerated, in 9 patients being necessary to lower the dose, due to myalgias and increase in muscle enzymes.

Comparative Evaluation of the Atheromatous Plaque Stability under Statin Therapy and Statin Therapy added to ACEI, respectively

The therapy with angiotensin-converting-enzyme inhibitor (ACEI) also has an anti-inflammatory effect, in addition to the antihypertensive effect, and by reducing oxidative stress plays a role in improving vascular endothelial dysfunction⁴⁴.

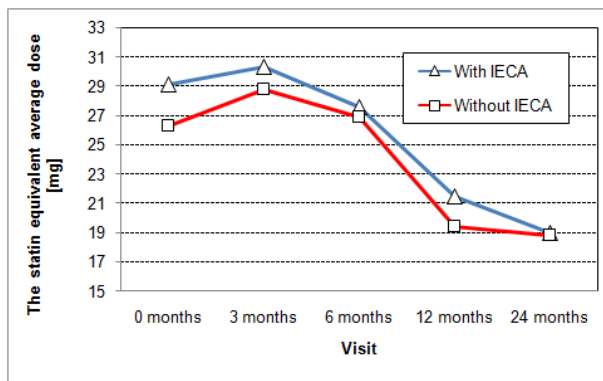


Figure 16. Variation of medium dose of statin prescribed for the two analyzed subgroups.

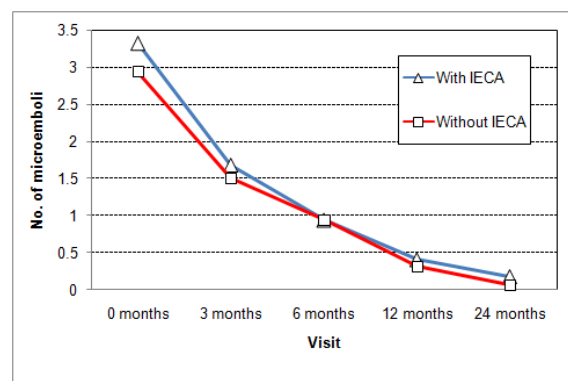


Figure 17. Variation of the microemboli number for the two analyzed subgroups.

It can be asserted that although the subgroup treated with ACEI had medium doses of statin slightly higher in the first 6 months of treatment, the addition of an angiotensin-converting-enzyme inhibitor to statin therapy is favourable due to the more accentuated reduction in the number of microemboli and normalization of biological samples related to lipid profile and inflammation. The parameters studied vary during the study but none of them (IMT, plaque thickness, microemboli, inflammation) changes statistically significant in the patients treated with ACEI compared to those without ACEI in their treatment.

The favourable effects of the combined therapy with ACEI and statin, relating to the reduction in the number of microemboli, improvement of lipid parameters and inflammatory syndrome, recommend the use of this association in patients with acute events and unstable atheromatous plaque.

Conclusions

1. CVA is an important health problem for the adult population in our country due to its increased incidence.

2. The pathological profile of the patient within the studied group is similar to that described in the specialized literature, in which the association of risk factors is in direct relation to vascular disease. Among these factors, high blood pressure is the most common followed by dyslipidemia, which has a key role in causing atherosclerosis.

3. Carotid atheromatosis is the main etiopathogenic factor for vascular ischemic cerebrovascular disease, the presence of unstable atheromatous plaques being responsible for arterial embolism.

4. HMG CoA reductase inhibitors (statins) are the most important class of drugs involved in the stabilization of the atheromatous plaque, through their lipid-lowering and pleiotropic effect.

5. The cervical-cerebral Doppler ultrasound is the investigation most commonly used for both diagnosis and monitoring of atheromatous plaque.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

6. Hypoechogetic, non-homogenous atheromatous plaques, with areas of bleeding and ulceration (type I, II and III) cause cerebrovascular events with increased risk of recurrence.

7. IMT is a marker of vascular suffering for patients with dyslipidemia and high blood pressure, being a screening method for cardiovascular diseases. It correlates with the age of the patient, associated pathology (diabetes and obesity which are major risk factors) and with the type of atheromatous plaque. IMT begins to decrease after 12 months of high-dose treatment, statistically significant decrease after 24 months, regardless of the type of statin. Medium-term treatment improves endothelial dysfunction.

8. Similarly to the observations in the specialized studies and within the doctoral dissertation, I found out that the instability of the plaque increases with the increase of its size.

9. Although on the medium term (12 months) statin therapy does not change the size of the atheromatous plaque, it slows the progression and after longer periods (24 months) leads to its regression. Statin therapy has been shown to be effective in stabilizing atheromatous plaques, through high-dose administration in the first year of treatment and maintenance of moderate doses for long periods.

10. The detection of microemboli by Transcranial Doppler is the most important method of identifying atheromatous plaque instability.

11. The stabilization of the atheromatous plaque by significantly lowering the number of microemboli and the recurrences depends on the dose and not on the type of statin. Their number does not influence the type of cerebrovascular event.

12. Recurrence is more often found in type II and III of plaque in association with the inflammatory syndrome, more commonly causing TIA, which supports the direct causal relation between the presence of microemboli and vascular accident.

13. Statins also have, due to their known pleiotropic effects, an anti-inflammatory effect, its intensity being dose-dependent. On a long term the decrease of the inflammatory syndrome was linked to atheromatous plaque involution (decrease in the number of microemboli and atheroma size).

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

14. The treatment with HMG CoA reductase inhibitors significantly improves lipoprotein electrophoresis values, regardless of the initial level of cholesterol, also acting on the cholesterol in the atheromatous plaque. The effect is dose-dependent, manifests right from the first months of treatment and is maintained throughout the duration of the treatment and may be intensified by non-pharmacologic therapeutic measures related to nutrition, lifestyle, physical activity.

15. Therapeutic doses recommended are proportional to the level of cholesterol, degree of instability of the plaque, risk of cardiovascular events and rate of recurrences. Their administration is made according to the applicable guidelines, taking into account the associated pathology.

16. This class of drugs has shown a good tolerability and safety. In the analysis of biological samples a relationship of direct influence was demonstrated between the dose and the level of muscle and liver enzymes, relationship that depends on the treatment and not on its length. Although some of the patients complained of headache, muscle cramps, muscle fatigue on exertion, it was not necessary to stop the treatment.

17. The treatment with ACEI does not significantly affect the stability of the atheromatous plaque.

18. Statin therapy provides a good compliance to the treatment due to the wide range of pharmaceutical products with different active substances but similar therapeutic effects (subject to compliance with the dose equivalence), possibility to purchase them under a reimbursable regime, easy administration.

19. Statins improve the quality of life of patients with cardiovascular risk by preventing cardiovascular diseases or recurrence of vascular events.

20. Diagnosing cardiovascular diseases and prescribing an individualized treatment requires the identification and monitoring of atheromatous plaques by Doppler ultrasound. The presence of microemboli as a marker of plaque vulnerability influences the dose and duration of statin treatment.

EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

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EFFECT OF STATIN ON ATHEROMATOUS PLAQUE STABILIZATION IN HEMODYNAMICALLY INSIGNIFICANT CAROTID ATHEROMATOSIS

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