Statins and stroke: potential mechanisms for neurovascular protection

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Summary. As the average human lifespan is increasing worldwide, ischemic stroke became one of the most important causes of mortality and morbidity, particularly in emerging countries. Significant decrease in the rates of first and recurrent stroke using statins has been established in large clinical trials and in systematic reviews and meta-analyses. Interestingly, observational studies reported that cholesterol levels were only weakly associated with ischemic stroke, suggesting that other potential mechanisms for vascular protection should be implicated. Indeed, beyond lipid changes, some properties of these drugs, related to inflammation, hemostasis, endothelial function, plaque stabilization, and more recently, to the mobilization of endothelial cells, have been proposed. In addition, recent meta-analysis also revealed that statins decrease systolic and diastolic blood pressure. Taken together, all these benefits can contribute for stroke prevention by statins.

Key words. Blood pressure. Endothelial progenitor cells. Hemostasis. Inflammation. Stroke. Statins.

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Prevention of strokes by statins based on large clinical trials

In 2005, the Cholesterol Treatment Trialists (CTT) collaborators published a meta-analysis of 14 randomized, placebo controlled studies using statins that were available at that time. They found 2,957 first strokes on these trials that included 90,056 individuals, and reported a significant 17% proportional reduction in the incidence of first stroke of any type among those receiving statins (RR 0.83, 99% CI 0.78–0.88, $p < 0.0001$) [1]. According to the authors, the overall reduction in stroke was mostly attributed to ischaemic cerebrovascular accident, which was reduced in 22% (RR 0.78, 99% CI 0.70-0.87, $p < 0.0001$) per mmol/L of LDL-cholesterol reduction [1]. During an average follow-up of 5 years, the use of statins was translated into eight (95% CI 4-12) fewer strokes per 1,000 subjects on secondary prevention for coronary heart disease, and five (95% CI 1-8) in those without known coronary disease, per mmol/L of LDL-cholesterol reduction [1]. The same investigators reported in 2008 the effects of statin treatment in 18,686 diabetic subjects from the same trials included in the meta-analysis. They found a 21% relative risk reduction for the first stroke for those on statin therapy (RR 0.79, 99% CI 0.67-0.93, $p = 0.0002$) [2].

In 2006, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was published and added new information on the role of statins on the secondary prevention of stroke [3]. This particular trial enrolled 4,731 patients with previous stroke or TIA which ocurred within one to six months prior to the study entry. All patients included had no previous history of coronary heart disease and were treated with atorvastatin 80 mg or placebo. After a median follow-up of 4.9 years, the primary objective of the study, a first fatal or nonfatal stroke, was reduced in 16% (adjusted hazard ratio 0.84, 95% CI 0.71-0.99, $p = 0.03$) [3]. Again, the benefit was due to a significant reduction on the ischemic stroke rate. Other benefits included a significant reduction on major coronary events (adjusted hazard ratio 0.65, 95% CI 0.49-0.87, $p = 0.003$), and major cardiovascular events (adjusted hazard ratio 0.80, 95% CI 0.69-0.92, $p = 0.002$) [3]. The benefit of statin treatment in the trial was demonstrated in the prevention of ischaemic stroke (hazard ratio 0.75, 95% CI 0.66-0.94), but there was an increase in the rate of hemorrhagic stroke (hazard ratio 1.66, 95% CI 1.08-2.55). No differences were seen between groups in the incidence of fatal hemorrhagic stroke (17 in the atorvastatin and 18 in the placebo group) as well as in the total mortality.

More recently, another important trial tested the benefit of statin treatment on stroke prevention among patients in primary prevention for cardiovascular disease. The JUPITER trial [4] evaluated the benefit of rosuvastatin 20 mg daily among

17,802 subjects with relatively normal baseline LDL-cholesterol levels (< 130 mg/dL), but who were at increased risk due to high levels of C-reactive protein (≥ 2 mg/L). After a median follow-up of 1.9 years an unexpected 48% reduction in the incidence of first fatal or non-fatal stroke was observed among those patients receiving statin therapy (hazard ratio 0.52, 95% CI 0.34-0.79, p = 0.002). The authors reported that the benefit was due to a 51% reduction in the rate of ischaemic stroke (hazard ratio 0.49, 95% CI 0.30-0.81, p = 0.004) with no difference between groups in the rates of hemorrhagic stroke.

After the JUPITER trial, Amarenco & Labreuch published an interesting review and meta-analysis on the effect of statins including 165,792 individuals [5]. According to the authors, for primary prevention of stroke, the relative risk of fatal and non-fatal strokes was decreased in 19% (RR 0.81, 95% CI 0.75-0.84, p < 0.0001), and for secondary prevention of stroke, the relative risk was reduced in 12% (RR 0.88, 95% CI 0.78-0.99, p = 0.003), among patients treated with statins. Considering all trials together there was a relative risk reduction in stroke of 18% (RR 0.82, 95% CI 0.77-0.87, p < 0.0001). For hemorrhagic stroke there was a non-significant effect of statin treatment in primary prevention (RR 0.81, 95% CI 0.60-1.08, p = 0.15). Conversely, there was a significant increase in secondary prevention for hemorrhagic stroke (RR 1.73, 95% CI 1.19-2.50, p = 0.004). Considering all these trials together (primary and secondary prevention), the authors found a non-significant effect of statin therapy in the relative risk for hemorrhagic stroke (RR 1.03, 95% CI 0.75-1.41, p = 0.88).

In another interesting meta-analysis high dose of atorvastatin (80 mg daily) was compared with standard statin doses among coronary heart disease patients. For this analysis, Bobadilla et al [6] included 25,709 subjects from five randomized statin studies and found a significant reduction in the stroke rates for those allocated to receive atorvastatin 80 mg (relative risk 0.83, 95% CI 0.72-0.96, p = 0.0121). The table shows the main findings and some characteristics of the clinical trials involving statins and stroke prevention.

Potential mechanisms linking statins to cerebrovascular protection

Lipids and stroke

In the Multiple Risk Factor Intervention Trial (MRFIT) [7], a positive association with ischemic stroke was observed with serum cholesterol levels. On the other hand, a study which enrolled 350,977 men, 35 to 57 years of age, with a six-year follow-up showed an inverse relation between serum cholesterol levels and death from hemorrhagic stroke. Subsequently, in the Copenhagen City Heart Study [8], an observational survey involving 19,698 adult men and women, 660 non-hemorrhagic and 33 hemorrhagic strokes were recorded. The authors reported a positive relation between total cholesterol levels with non-hemorrhagic events. In addition, a negative association was found between high density lipoprotein (HDL) cholesterol levels and non-hemorrhagic stroke [8]. In the same study, high non-fasting triglycerides levels were associated with ischemic stroke [9].

Another important cohort in the northwestern Germany (the Prospective Cardiovascular Muenster Study), also examined the major risk factors related to the incidence of stroke [10]. After an average follow-up of 7.2 years among 12,866 men, the authors reported an increased incidence of first stroke with age. After adjustments, the relative risk for stroke was associated with systolic blood pressure, smoking status, hypertension and diabetes mellitus. No clear relationship with cholesterol levels was seen in this study. Interestingly, in the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, the LDL cholesterol levels were not predictors of stroke, even among those patients with atherosclerotic carotid disease [11]. In fact, based on this trial, only baseline HDL cholesterol was related with the outcome of stroke [12].

Taken together, epidemiological data suggest a positive and weak association between non-hemorrhagic stroke and both total and LDL-cholesterol levels, and an inverse relation between total- and LDL-cholesterol levels with hemorrhagic stroke. An inverse relation between HDL-cholesterol and stroke was also observed, as well as a positive association between non-fasting triglycerides levels and ischemic stroke. Based on these aspects, and taking into account that statins act mainly on LDL-cholesterol levels, these observed benefits on stroke prevention seem not to be related solely to lipid changes, but other non-lipid mechanisms induced by statins may be involved in stroke prevention.

Effects of statins beyond lipid changes

In recent years, some important properties of these drugs beyond cholesterol reduction have been reported to explain their entire spectrum of benefits on atherosclerosis. On this regard, improvement of

Table. Statin therapy and stroke prevention [1-5].

Study	Any stroke	Ischaemic stroke	Hemorrhagic stroke
CTT [a], *n* = 90,056	↓ 17% RR = 0.83 CI 95% = 0.78-0.88	↓ 22% RR = 0.78 CI 99% = 0.7-0.87	↑ 5% RR = 1.05 CI 99% = 0.78-1.41
SPARCL *n* = 4,731 (atorvastatin)	↓ 16% RR = 0.84 CI 95% = 0.71-0.99	↓ 22% RR = 0.78 CI 95% = 0.66-0.94	↑ 66% RR = 1.66 CI 95% = 1.08-2.55
JUPITER *n* = 17,802 (rosuvastatin)	↓ 48% RR = 0.52 CI 95% = 0.34-0.79	↓ 51% RR = 0.49 CI 95% = 0.3-0.81	↓ 33% RR = 0.67 CI 95% = 0.24-1.88
Amarenco [b] *n* = 165,792	↓ 18% RR = 0.82 CI 95% = 0.77-0.87	No available	Not significative RR = 1.03 CI 95% = 0.75-1.41
Bobadilla [c] *n* = 25,799 (atorvastatin)	↓ 17% RR = 0.83 CI 95% = 0.72-0.96		

CI = confidence interval. [a] Includes: 4S (Scandinavian Simvastatin Survival Study), WOSCOPS (West of Scotland Coronary Prevention Study), CARE (Cholesterol And Recurrent Events); Post-CABG (Post Coronary Artery Bypass Grafting), AFCAPS/TexCAPS (Air Force-Texas Coronary Atherosclerosis Prevention Study), LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease), GISSI prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico), LIPS (Lescol Intervention Prevention Study), HPS (Heart Protection Study), PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), ALLHAT-LLT (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm), ALERT (Assessment of Lescol in Renal Transplantation study), and CARDS (Collaborative Atorvastatin Diabetes Study), CTT (Cholesterol Treatment Trialists); SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin); [b] Includes: SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, JUPITER, ASPEN (Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus), MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese), IDEAL ((Incremental Decrease in End Points Though Aggressive Lipid), TNT (Treating to New Targets), ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events), CARDS; PROVE-IT, A to Z ((Aggrastat to Zocor); ASCOTT-LLT, ALLHAT-LLT, GREACE (Greek Atorvastatin and Coronary-Heart-Disease Evaluation), HPS, PROSPER, MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), GISSI, AFCAPS/TexCAPS, LIPID, Post-CABG, CARE, WOSCOPS, 4S; [c] Includes TNT, IDEAL, PROVE-IT, ALLIANCE, VBSS.

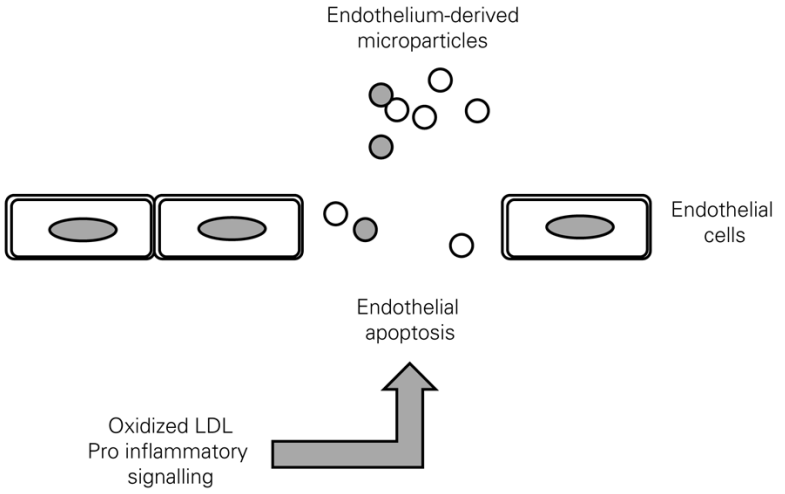
endothelial function, and reduction on markers of inflammation and hemostasis, seems to be key mechanisms of vascular protection. Furthermore, these pharmacological agents, by modulating the innate and adaptive immunity, can affect the healing process following the vascular injury due to several risk factors. In fact, these so-called pleiotropic effects of statins constitute a fascinating field of investigation in atherosclerosis. Some of these properties are detailed in this review.

Mechanisms for atherothrombotic events

The major characteristics of the vulnerable plaque were reported in the last decade by Libby [13,14] and confirmed by numerous studies of imaging and pathology. The rupture of these plaques is responsible for 75% of coronary thrombosis related to myocardial infarction and death, and 90% of ischemic stroke [15]. The lipid core of these vulnerable coronary plaques is greater than that of stable lesions, corresponding to 29-43% of atheroma area, and in the site of plaque rupture, there is a high concentration of inflammatory cells, mainly macrophages. In patients with symptomatic carotid disease the lipid core constitutes 40% of the atheroma [15].

The pathophysiology of atherosclerosis is still poorly understood, but the deposition of cholesterol forming the atherosclerotic plaque in the intima seems to share similar vascular responses, even when associated with a variety of different risk factors such as diabetes, hypertension, smoking habit or dyslipidemias. These common aspects include: endothelial dysfunction, oxidized lipoproteins, inflammatory cells in the intima (macrophages, lymphocytes, mast cells), neovascularization, and intraplaque hemorrhage. The thrombotic event is usually associated with plaque rupture or endothe-

Figure 1. Uncontrolled risk factors can promote oxidation of lipoproteins and trigger a pro inflammatory signalling. Thus, apoptosis of endothelial cells can occur, leading to the formation of endothelial derived microparticles. These microparticles are highly thrombogenic particles and can contribute for vascular thrombosis.



lial erosion [16,17]. The plaques prone to rupture not necessarily are obstructives, and, in fact, coronary and cerebrovascular events can occur even with small degree of vascular stenosis [18,19]. Indeed, the presence of intraplaque hemorrhage, neovascularization and vasa vasorum development, but not the degree of restenosis, seem to be the determinant components of plaques prone to atherothrombotic complications [20,21]. An important aspect is the frequent concomitant presence of atherosclerosis in more than one site (coronary, cerebrovascular, and peripheral) [22,23].

During many years cardiovascular events were associated with the degree of vascular stenosis, and modest attention was given to the plaque components. Nowadays, it has been recognized that many aspects of the vulnerable plaques, such as a variety of cells involved in the innate and adaptive immunity plays an important role in the local thrombogenicity, endothelial activation and inflammatory signalling [24,25]. In fact, it has been recognized that oxidized lipoproteins can induce the release of antibodies (anti oxLDL Abs) by B lymphocytes that can complex with modified lipoproteins. These autoantibodies seem to have a protective role in atherosclerosis, as was suggested by the increased titers of the Abs among stable patients [26] and after blood pressure control in hypertensive patients [27].

In some regions of the vasculature there are profound alterations in the antithrombotic endothelial properties, reducing the ability of these cells to produce endogenous fibrinolysis, or to avoid platelet activation. Furthermore, the presence of some inflammatory cells in the intima increases the release of pro-thrombotic products (Fig. 1).

In addition to plaque rupture, which occurs mainly in plaques with thin fibrous cap and large lipid core, endothelial erosion is another common mechanism for thrombotic events, particularly among women, diabetic subjects and in the elderly [28,29].

Other crucial components for the atherothrombotic event are not in the plaques, but in the blood stream. The presence of systemic inflammation, characterized by high levels of circulating interleukins and several acute-phase proteins, including some markers of coagulation cascade activation, increases the risk for thrombotic events [30].

All the classical cardiovascular risk factors contribute to some extent for the systemic and local inflammation, which triggers endothelial activation or its apoptosis. On the other hand, the ability to replace the apoptotic or senescent endothelium by endothelial progenitor cells mobilized from bone marrow is also diminished in the presence of these classical risk factors [31-35]. The fragmentation of the endothelium not only creates a region prone for local thrombosis, but also releases microparticles in the blood stream that are highly thrombogenic. Therefore, our current vision of the pathophysiology of atherothrombosis involves many systemic and local components. How statins can modify this scenario?

Pleiotropic effects of statins

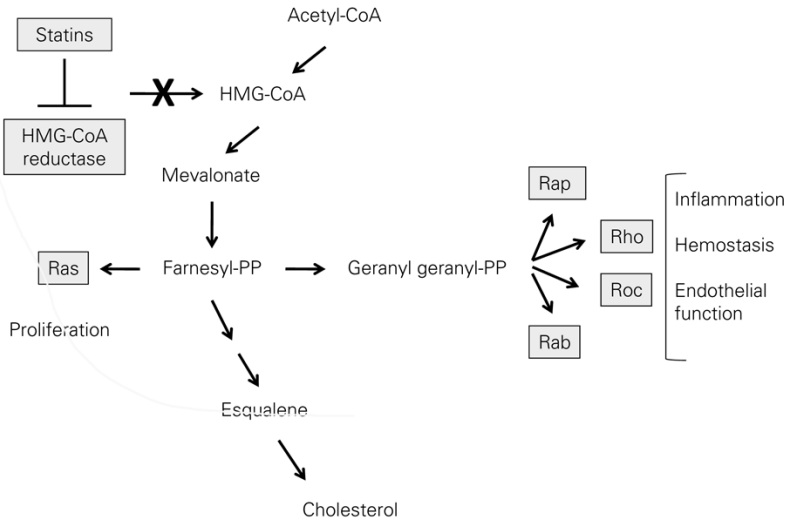
The majority effects of statins beyond cholesterol synthesis reduction are, in fact, correlated with the inhibition of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase.

All statins share part of their chemical structure with the HMG-CoA, the substrate of the enzyme. Therefore, statins act as alternative substrate for the enzyme (HMG-CoA reductase) [36]. Statins of the last generation (atorvastatin, rosuvastatin) are more effective than the first ones, because they have more chemical groups in their molecules which increase duration of interaction with the enzyme through hydrogen bonds [37].

The endogenous cholesterol synthesis occurs after several steps following the activation of the cascade from the interaction of HMG-CoA re-

ductase with its natural substrate. Due to the inhibition of the cholesterol synthesis by statins, some intermediate compounds are less expressed (farnesyl pyrophosphate and geranylgeranyl pyrophosphate), which can explain the antiatherosclerotic properties of these drugs (Fig. 2). By the lower bioavailability of these intermediate substances, some small proteins present in the cytosol are also less translocated to the cell membrane, determining lower transcription of genes related to inflammation and hemostasis [38,39]. In addition, through the same mechanisms, stabilization of the endothelium is achieved, with release of nitric oxide, and improvement on endothelium-mediated vasoreactivity (Fig. 3).

Figura 2. Endogenous cholesterol synthesis. Statins reduce the expression of intermediate compounds, such as farnesyl pyrophosphate or geranylgeranyl pyrophosphate, by the inhibition of hydroxymethyl glutaryl CoA reductase. The consequence is a lower translocation of small signalling proteins (Rho, Ras, Rap, Roc, Rab) to the cell membrane, reducing the formation of several proteins involved in the coagulation cascade, inflammation or proliferation. In addition, through the inhibition of the complex Rho/Rhokinase there is an improvement in the endothelial function due to the higher formation of nitric oxide.



Endothelial progenitor cells and stroke

Other potential mechanism for vascular protection provided by statins is the ability of these compounds to mobilize endothelial progenitor cells (EPC).

The bone marrow is the main source of EPC in the adult. The lower mobilization of these cells in the bloodstream is related to cardiovascular diseases, and individuals with reduced circulating EPC are at higher risk for coronary artery disease [40,41]. The recruitment can be stimulated by pro-angiogenic citokines, such as VEGF (Vascular Endothelial Growth Factor) and SDF1 (Stromal Cell-Derived Factor-1), produced by hypoxic areas or in response to vascular damage [42].

Due to the extreme scarcity in the peripheral blood, an important step in the identification of EPC and circulating (mature) endothelial cells (CEC) has been the development of sensitive techniques for the detection of rare events, based on immunodetection using fluorescent antibodies [43]. The EPC express different markers of surface, depending on differentiation stage. When immature, these cells express hematopoietic markers, such as CD133, CD34, KDR and monocyte/macrophage markers, as the CD11b and the CD14 [43,44]. In mature EPC the CD133 is not expressed, and CD31+, and other typical markers of endothelial cells, such as the Von Willebrand factor (vWF), VE-cadherin, Tie-2, CD146 and E-selectin characterize these cells at this stage [45-47].

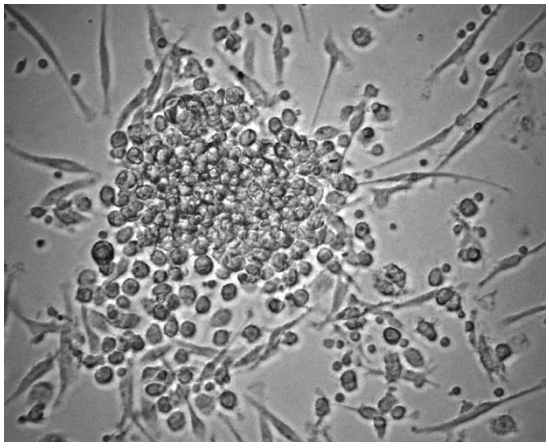
The use of EPC as a tool for evaluating therapeutic angiogenesis or vasculogenesis constitutes a new perspective for monitoring patients with cardiovascular diseases. Depletion of circulating EPC is associated with endothelial dysfunction, an early event in the atherogenesis process. In addition, the lack of EPC mobilization seems to impair the new vessel formation in ischemic areas, as a late event, contributing to clinic manifestations of atherosclerosis and cardiovascular disease progression.

The EPC measurement emerges as a promising cardiovascular biomarker, based on its association with cardiovascular risk and extension of atherosclerosis [48].

Stroke and endothelial progenitor cells

For primary or secondary stroke prevention, some benefits reported with statins can be related to the improvement of the balance between EPC mobilization and endothelial apoptosis. On this regard, recent studies have shown that EPC are reduced in subjects with acute stroke [49], and the extension of stroke might be reduced with increased amount of EPC [50]. Patients with a higher number of circulating EPC after stroke have better outcomes than those with fewer EPC, suggesting that EPC may serve as a new marker for stroke outcomes. Furthermore, EPC also participate in revascularization after focal cerebral ischemia, and isolated EPC from bone marrow (BM) attenuate ischemic injury in rats. However, it is unclear whether revasculariza-

Figure 3. Endothelial cell culture. Example of the typical aspect of endothelial cells proliferation, observed after nine days of blood collection of patient in chronic statin use. Statin use is associated with both higher degree of cell proliferation and functionally.



tion mediated by EPC improves long-term neurological outcomes after ischemic stroke.

Stroke involves an intrincate cascade of events involving cerebral ischemia; altered blood flow; disruption, inflammation, neuronal necrosis, apoptosis of the blood-brain barrier; and neurological dysfunction. The mechanisms involved in the mobilization of EPC are not clear, but vascular trauma and tissue ischemia appear to facilitate EPC mobilization to the peripheral pool, in part by the release of cytokines and vascular endothelial growth factor.

There are recent studies evaluating the relation between endothelial progenitor cells EPC and stroke, and EPC can be a marker of future events in atherosclerotic stroke and a marker of the endothelial repair mechanism. Sobrino et al [51] observed an increase of EPC cluster numbers 7 and 90 days after a stroke, and the increased number of EPC was related to a good outcome. Same findings were observed in other studies, reporting an increased amount of CD34+ cells 7 to 14 days after an ischemic stroke [52] and lower EPC cells in the early period of patients with acute stroke in comparison with control subjects [53].

Experimental administration of EPC in animals induces the formation of new blood vessels and also increases blood flow in cerebral ischemia, which opens new perspectives in neovascularization by agents that mobilize these cells. However, the beneficial effects of EPC in the brain are probably not limited to neovascularization. Indeed, an observational study in rats with experimental stroke showed neovascularization related to neurogenesis (from neural progenitor cells present in the brain), and also to migration of these neural progenitor cells along the newly formed vessels [54].

An interesting study found a direct correlation between homocysteine and EPC colony counts in stroke patients, indicating a possible role of homocysteine in affecting the integrity of the vascular system and its relationship to EPC [55].

Increased mobilization of endothelial progenitor cells by statins

Beyond favourable lipid changes and some benefits on inflammation and hemostasis, statin use can rapidly increase the mobilization of endothelial cells. Contributing to endotelial repair, these agents add new and important mechanisms for vascular protection. These benefits seem to be largely independent of cholesterol levels, as suggested by the comparison of two hypolipidemic agents, ezetimibe and simvastatin on endothelial cells mobilization after 4 weeks of therapy, achieving similar LDL-cholesterol reduction [56]. Figure 3 shows the typical morphology of endothelial cells after 9 days of culture in patient under chronic statin therapy.

Increased amount of endothelial progenitor cells was observed in patients receiving atorvastatin 3-week prior to cardiopulmonar bypass surgery [57]. Higher levels of endothelial progenitor cells were observed since the preoperative period and the statin therapy also reduced inflammatory markers measured in the postoperative period. These benefits were not correlated with changes in serum cholesterol levels [57].

The effects of LDL-cholesterol reduction on the mobilization of endothelial progenitor cells were recently compared among coronary heart disease patients by three different regimens of hypolipidemic therapy: de novo atorvastatin, ezetimibe (an inhibitor of cholesterol absorption) add-on chronic statin therapy, and dose escalation of atorvastatin over four weeks [58]. Treatment with de novo or titrated doses of atorvastatin reduced circulating apoptotic endothelial cells by 50% and doubled the amount of endothelial progenitor cells. Conversely, ezetimibe did not modify the amount of mature or progenitor endothelial cells, despite significant reduction in the cholesterol serum levels [58]. Thus, mobilization of progenitor endothelial cells and reduction in the endothelial erosion were related to the pleiotropic effects of statins, and not influenced by lipid changes.

Effects of statins on blood pressure

More than half of strokes can be attributed to blood pressure elevation [59] and the relative risk for a first stroke increases, continuously above a blood pressure of 115/75 mmHg [60]. The rates of recurrent stroke are also significantly influenced by blood pressure levels [61,62]. Indeed, based on meta-analysis of nine randomized studies, even small reductions on blood pressure (1-3 mmHg) are associated with outstanding reduction in the risk of stroke (20-30%) [63]. Thus, one possible mechanism of stroke prevention by statins could be related to the ability of these drugs to reduce blood pressure.

Recently, large clinical trials and meta-analysis confirmed that a small, but significant reduction on blood pressure was observed among statin users.

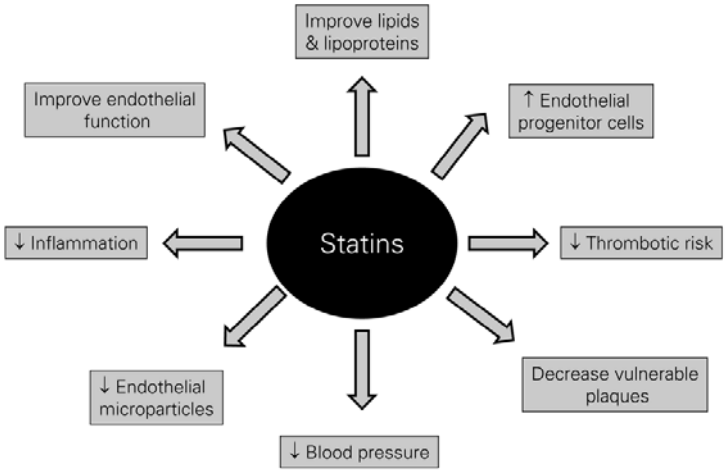
Strazzullo et al [64] analised 20 statin trials in which concomitant antihypertensive treatment was not changed throughout the study. This meta-analysis showed that statin therapy reduced systolic blood pressure (mean difference: –1.9 mmHg; 95% CI: –3.8 to –0.1). The authors reported greater effect of statins for those patients with baseline systolic blood pressure > 130 mmHg, and the blood pressure response was not related to changes on serum cholesterol.

The effects of statins on blood pressure were examined in the UCSD (University of California, San Diego) Statin Study [65]. The authors tested the effects of simvastatin 20 mg, pravastatin 40 mg, or placebo in 973 men and women for 6 months. A small, but significant decrease in blood pressure was observed for systolic blood pressure (–2.2 mmHg, $p = 0.02$) as well as for diastolic blood pressure (–2.4 mmHg, $p < 0.001$) in statin users.

Recently, the effects of statin use were reported in the National Health and Nutrition Examination Survey (NHANES) [66]. The study showed that systolic blood pressure was on average 1.8 mmHg lower in statin users versus nonusers ($p = 0.05$). These benefits of statins on systolic blood pressure were restricted to hypertensive patients using antihypertensive therapy. Statin users also had lower diastolic blood pressure, –1.9 mmHg on average, regardless of antihypertensive therapy.

Summarizing the blood pressure effects, the use of statins seems related to a small but significant reduction on blood pressure. This effect is greater among hypertensive patients and is not substantially influenced by changes in cholesterol levels. The possible mechanisms involved include: restoration of endothelial function, decrease in inflammation (hypertension is usually preceded by elevation on serum markers of inflammation, e.g. C-reactive protein) [67-69], decline in the renin-angiotensin system activation [70], and reduction in the carotid pressure waveform [71]. All these mechanisms may be involved in the stroke prevention, beyond lipid changes by statins.

Figure 4. Major mechanisms involved in the prevention of strokes by statins.



In conclusion, statin use emerges as a usefulness antiatherosclerotic strategy to reduce stroke rates. Primarily considered a hypolipidemic agent, this class of drugs simultaneously is able to attenuate multiple mechanisms related to plaque formation and its desestabilization. Figure 4 summarizes the multiple pathways involved for the cardiovascular protection following the therapy with statins. It is also of worth to remind that concomitant disease in other vascular territories is very common in cerebrovascular disease, and the use of statins can also prevent other cardiovascular events, such as the complications of coronary heart disease and peripheral vascular disease.

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Estatinas y accidente cerebrovascular: posibles mecanismos de acción de la protección neurovascular

Resumen. Como la esperanza de vida media de los seres humanos está aumentando en todo el mundo, el accidente cerebrovascular isquémico se ha convertido en una de las causas más importantes de morbimortalidad, especialmente en los países emergentes. Se ha establecido un descenso significativo en las tasas del primer accidente cerebrovascular y del accidente cerebrovascular recurrente con el uso de estatinas en ensayos clínicos grandes y en metaanálisis y revisiones sistemáticas. Curiosamente, los estudios de observación describieron que los niveles de colesterol estaban sólo débilmente asociados al accidente cerebrovascular isquémico, lo que sugiere que debe haber otros posibles mecanismos implicados en la protección vascular. De hecho, más allá de los cambios en los lípidos, se han propuesto algunas propiedades de estos medicamentos relativas a la inflamación, hemostasia, función endotelial, estabilización de las placas de ateroma y, más recientemente, a la movilización de las células endoteliales. Asimismo, un metaanálisis reciente también puso de manifiesto que las estatinas reducen la presión arterial sistólica y diastólica. En general, todos estos beneficios pueden contribuir a la prevención de los accidentes cerebrovasculares mediante el uso de estatinas.

Palabras clave. Accidente cerebrovascular. Células madre endoteliales. Estatinas. Hemostasia. Inflamación. Presión arterial.