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Review

Statins: pros and cons

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ABSTRACT

Statins inhibit the critical step of cholesterol synthesis in which 3-hydroxy-3-methylglutaryl coenzyme A (HMGC) is transformed to mevalonate by the enzyme HMGC reductase. By doing so, they have a potent lipid-lowering effect that reduces cardiovascular risk and decreases mortality. Since the mevalonate pathway also influences endothelial function, the inflammatory response, and coagulation, the effects of statins reach well beyond their cholesterol lowering properties. As with all drugs, statins may have adverse effects; these include musculoskeletal symptoms, increased risk of diabetes, and higher rates of hemorrhagic stroke. However, the frequency of adverse effects is extremely low and, in selected patient populations, the benefits of statins considerably outweigh the potential risks.

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Pros y contras de las estatinas

Palabras clave:
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RESUMEN

Las estatinas inhiben el paso crítico de la síntesis del colesterol, donde la enzima 3-hidroxi-3-metilglutaril A (HMGC) se transforma en mevalonato por medio de la enzima HMGC reductasa. Al hacerlo, tiene un potente efecto reductor de lípidos que reduce el riesgo cardiovascular y disminuye la mortalidad. Como la vía del mevalonato influye también en la función endotelial, la respuesta inflamatoria, y la coagulación, los efectos de las estatinas van más allá de sus propiedades reductoras del colesterol. Como todos los fármacos, las estatinas pueden tener efectos adversos que incluyen síntomas musculoesqueléticos, incremento del riesgo de diabetes y tasas superiores de accidentes hemorrágicos. Sin embargo, la frecuencia de estos efectos adversos es extremadamente baja y, en poblaciones seleccionadas de pacientes, los beneficios de las estatinas superan con creces los riesgos potenciales.

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In 1976, the Japanese microbiologist Akira Endo discovered the first statin as a product of the fungus *Penicillium citrinum* that inhibited the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR); this first molecule was named compactin.[1] Subsequently, researchers at Merck Research Laboratory discovered another HMGCR inhibitor derived from *Aspergillus terrus* that was originally named mevinolin and later known as lovastatin.[2] This molecule was the first statin to be approved by the FDA. Since then, other drugs from the same family have been synthesized, revolutionizing the management of cardiovascular diseases.

Statins block the rate limiting step of cholesterol synthesis in which 3-hydroxy-3-methylglutaryl coenzyme A (HMGC) is transformed to mevalonate by the enzyme HMGCR. However, the cholesterol biosynthetic pathway is also involved in the synthesis of dolichols, the production of ubiquinone (coenzyme Q10), and in the process of prenylation, an important post-transcriptional protein modification. Of note, dolichols are required for glycoprotein synthesis[3] and ubiquinone plays an important role in muscle cell energy production.[4] Furthermore, prenylation is required for activation of numerous proteins, including members of the GTPase family of molecular switches (e.g. CDC42, RAC or RHO), which have crucial roles in controlling multiple signaling pathways.[5]

While lowering cholesterol levels is the main therapeutic effect desired with statin administration, decreased production of other

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downstream products of the mevalonate pathway may explain other effects, both beneficial and deleterious, of these drugs. In this review, we will discuss the available evidence regarding the pros and cons of statins.

Pros of statins

Lipid lowering effect

Cardiovascular disease (CVD) is currently one of the most important health problems in the world, causing one-third of all global deaths (17.3 million deaths per year).[6]

In the early 20th century, cholesterol plaques were found within the coronary arteries of patients who had died after suffering from angina pectoris.[7] Coincidentally, in the period from 1900 to 1960, the percentage of deaths due to coronary heart disease (CHD) increased from 10% to 40%. However, little was known at that time about the pathogenesis or risk factors of the disease.[8] For this reason, in 1948, a massive cohort study was initiated in Framingham, Massachusetts that was designed to define the risk factors for CHD. This study revealed that increased LDL levels are one of the most important risk factors in the development of CHD.[9]

Before statins were commercialized, there were clinical trials showing that diverse methods to lower the cholesterol levels, such as bypass surgery, cholesterol-lowering diets or drugs, could reduce the rates of myocardial infarction and coronary death. Moreover, the magnitude of this reduction was proportional to the degree of cholesterol lowering.[10,11]

Statins were markedly more efficacious in lowering LDL levels than previously available methods and the beneficial effects of lowering cholesterol levels with statins were confirmed in studies evaluating primary and secondary prevention of CVD. In fact, meta-analysis including previous clinical trials on the cardiovascular effects of statins found similar proportional reductions in the risk of developing new major vascular or coronary events in patients regardless of their age, sex, cholesterol levels, presence of diabetes, hypertension, previous myocardial infarction or other coronary heart diseases.[12]

Thus, it is estimated that each mmol/L of LDL reduction decreases by 22% the rate of major vascular events, by 14% the vascular mortality and by 10% the all-cause mortality per year. As an example, 40 mg of atorvastatin may decrease LDL levels more than 50% (e.g. from >4 mmol/L to ≈2 mmol/L). Thus, lowering LDL cholesterol by 2 mmol/L for 5 years in 10,000 patients would reduce the rate of major vascular events by 10% in secondary prevention (in patients at high risk of recurrent stroke or heart attack) and by 5% in primary prevention (patients at lower risk).[13]

Different statins have distinct properties, with pravastatin and simvastatin providing less LDL-lowering power (25–35% reduction at 20 mg dosing) than newer statins, like atorvastatin and rosuvastatin (40–50% reduction at 20 mg dosing).[14]

The reduction of LDL levels is independent of the patient characteristics and, on average, doubling the dose of any given statin reduces the LDL levels by about 6 percentage points.[14–16]

Statins confer cardiovascular protection not only by reducing the cholesterol levels but also by decreasing LDL-cholesterol oxidation, promoting the stabilization of the atheroma plaque, inhibiting endothelial dysfunction and vascular smooth muscle proliferation, and reducing platelet activity.

Pleiotropic effects

Atherosclerosis is a complex pathogenic process in which endothelial dysfunction, inflammation, and clot formation all play a role. As mentioned before, in addition to lowering cholesterol levels, statins inhibit other downstream products of the mevalonate pathway, causing the so-called pleiotropic effects. By way of these pleiotropic effects, statins modulate virtually all known mechanisms of atherosclerosis and show beneficial effects beyond the cardiovascular system.

Improvement of endothelial function

Endothelial dysfunction represents one of the first steps in pathogenesis of atherosclerosis and can be caused by known risk factors for cardiovascular disease. For example, hypertension, smoking, and high blood sugar levels can all impair normal vasodilatation, which is mediated by nitric oxide (NO). Statins inhibit the prenylation of Rac and Rho proteins[17] which, in turn, leads to increased expression of endothelium-derived nitric oxide synthetase (eNOS). With increased eNOS expression, nitric oxide production in the endothelium is increased and vasodilatation is promoted.[18]

Anti-inflammatory effects

After the endothelium is injured, the atherosclerotic plaque is infiltrated by inflammatory cells. Statins can inhibit inflammation through their demonstrated ability to reduce the production of inflammatory markers like the C-reactive protein (CRP) or serum amyloid A (SAA), interleukins, and adhesion molecules such as intracellular adhesion molecule (ICAM-I); each of these have been associated with the development and recurrence of cardiovascular events.[19,20]

Interestingly, pravastatin provides even greater risk reduction in patients with high risk of coronary events and elevated SAA and CRP than it does in patients with the same cardiovascular risk but normal levels of inflammatory markers.[19] This observation supports the notion that statins reduce risk not only by lowering cholesterol, but also by inhibiting inflammation. In this regard, it is noteworthy that both atorvastatin and simvastatin can reduce CRP levels,[21] even in patients without hyperlipidemia,[22] suggesting that statins may be useful in patients with normal LDL but elevated inflammatory markers.

Immunomodulatory effects

There is anecdotal evidence suggesting that statins may show anti-inflammatory and immunomodulatory activity in cardiac transplant rejection and several autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, lupus, vasculitis or systemic sclerosis, among others.[23]

Immunomodulatory properties of statins are multifactorial. In the first place, statins may decrease antigen presentation and T cell activation by restricting expression of the major histocompatibility complex class II (MHC-II) as well as reducing the cell-surface expression of other immunoregulatory molecules, including CD3, CD4, CD8, CD28, CD40, CD80 and CD54. Secondly, in vitro and in vivo studies support that statins may impair T-lymphocyte and natural-killer cell proliferation and cytotoxicity. Finally, statins decrease the expression of cellular adhesion molecules on leukocytes and endothelial cells leading to an impairment on cell adhesion and migration to the inflamed areas.[23]

Anti-thrombotic effect

Finally, the last step in atherosclerosis occurs when the endothelium is disrupted and a blood clot is formed, impairing blood flow. Statins may impair blood clot formation by reducing the expression of tissue factor and platelet aggregation, diminishing the creation of thrombin and the expression of its receptor on the platelet surface. Furthermore, the levels and activity of procoagulant factors, including fibrinogen, and factors V, VII and XIII, decrease as well during statin treatment.

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In addition to blocking clot formation, statins promote clot destruction by decreasing plasminogen activator inhibitor 1 (PA1-1)[24,25] levels and promoting the fibrinolytic enzyme plasminogen. The anti-coagulant properties of statins were demonstrated in the JUPITER study, which revealed a decreased rate if peripheral venous thromboembolism in patients taking atorvastatin.[26] Subsequently, a meta-analysis showed a 30–40% decrease of venous and pulmonary thromboembolism in patients taking statins.[27]

Also, related to both the anti-thrombotic and also the anti-inflammatory effects of statins, there is in vitro and in vivo evidence suggesting that statins may decrease the risk of thrombosis in patients with the antiphospholipid syndrome.[28,29]

Other beneficial effects attributed to statin therapy

In addition to their known cardiovascular and anti-inflammatory effects, statins have been credited with having other beneficial properties. For example, small randomized trials have suggested that statins may reduce the rate of postoperative atrial fibrillation following cardiac surgery by as much as 50%. Furthermore, observational studies have suggested that statins may have improve outcomes in patients with a wide range of conditions, including chronic obstructive lung disease, acute respiratory distress syndrome and pneumonia. However, the causal role of statins in achieving these benefits remains to be proven.[16]

Cons of statins

Notwithstanding the unquestionable benefits of statins in patients at risk for cardiovascular events, they also have the potential to cause side effects. The two best documented side effects in observational studies and clinical trials are an increased risk of myopathy and an increased incidence of diabetes. There is also some reliable evidence that statins increase the risk of hemorrhagic stroke. Other side effects, such as the potential to impair memory and cognition, promote cataract formation, and/or compromise kidney outcomes have been proposed, but not convincingly demonstrated. In the following pages, we will summarize the evidence that statins may be associated with each of these side effects.

Myopathy

Evidence to date indicates that statins can cause either self-limited myotoxicity, presumably due to the direct effect of statins in the muscle, or an autoimmune myopathy associated with autoantibodies targeting HMGCR.

Direct myotoxicity is a rare condition with an estimated accumulated incidence of about 10–20 cases per 10,000 statin-treated patients per year.[30] It is characterized by its resolution after stopping statin treatment, it is dose-dependent, and it can be of variable severity, ranging from isolated muscle pain to severe rhabdomyolysis leading to renal failure.

The pathological mechanisms underlying the myotoxicity of statins are not well understood. However, it has been suggested that statins could cause muscle damage by decreasing the production of ubiquinone, a protein in charge of stabilizing the cell membrane that also plays an important role in the mitochondrial respiratory chain[31]; increasing levels of sterols in the muscle fibers, which can increase the toxic effects of statins in the muscle[32] or related with the overexpression of artrogin-1, a key gen involved in skeletal muscle atrophy.[33]

The prevalence of musculoskeletal pain has been reported in observational studies to be 3–33% higher in patients taking statins.[34,35] However, further meta-analyses from randomized clinical trials have shown that these rates are closer to an absolute excess of 0.3% or, alternatively, a range from zero to 20 cases per 10,000 years of treatment, concluding that most cases of statin myalgia found in observational studies were not causally associated with statin treatment.[30] This is important to be taken into account in clinical practice when facing patients on statin treatment with musculoskeletal pain and no elevations of the CK levels.

Just around 1 case in 10,000 patients treated with statins each year will develop substantial elevations in creatine kinase (CK) levels and just about 2–3 per 100,000 patients will develop rhabdomyolysis with extremely high CK levels, myoglobinemia, myoglobinuria and acute renal failure.[30] However, the risk of statin myotoxicity may increase substantially when statins are used in combination with other drugs that affect their metabolism, specially inhibitors of cytochrome P450. Also, there are populations (people from Asian origin), and individuals (those with functional variation in the SLCO1B1 gene) that may be at a higher risk of developing this adverse effect.[36–38]

Alternatively, it has been recently found that a very small fraction of patients taking statins, approximately 2–3 per 100,000 patients treated per year, may develop autoimmune myopathy.[39] This myopathy is characterized by proximal muscle weakness, evidence of muscle-cell necrosis on the muscle biopsy and the presence of autoantibodies against HMGCR.[40,41] Characteristically, this type of myopathy does not revert after stopping statin administration, requiring treatment with immunosuppressive therapy. Anti-HMGCR associated myopathy is more common in patients exposed to prescription statins (92% of them in some studies), but can also happen in statin-unexposed patients.[42] To date, it is unknown if the disease in statin-unexposed patients is triggered by an unrelated environmental factor or by statins coming from non-prescribed sources of statins, such as some types of fungus (like the oyster mushroom), red yeast rice, or pu-erh tea. Of note, the class II HLA allele DRB1*11:01 is a potent immunogenetic risk factor associated with developing statin-associated autoimmune myopathy.[43]

Diabetes

Large randomized clinical trials have demonstrated an increased risk of developing diabetes mellitus in patients taking statins. The attributable excess risk of developing diabetes has been estimated to be about 10–20 per 10,000 patients treated per year, similar to the risk of developing a significant myopathy.[44]

The risk of diabetes is proportional to the dose of statins used and it appears soon after starting statin therapy, stabilizing afterwards. It occurs mainly among patients with other risk factors to develop diabetes (elevated body–mass index, impaired fasting glucose or high HbA_{1c}).[44]

The pathogenesis of statins causing diabetes is unknown. However, it has been hypothesized that this side effect might be related to the lowering of LDL cholesterol[45] or that the increasing number of LDL receptors induced by statins may enable more cholesterol to enter the pancreatic cells, damaging them.[46]

Notwithstanding this, the reduction of the cardiovascular risk induced by statin administration compensates any increase in diabetes-related morbidity.

Hemorrhagic stroke

Observational studies suggested that patients treated with statins may have an increased risk of hemorrhagic stroke. Blood cholesterol levels are negatively associated with the rates of hemorrhagic stroke, especially in patients with concomitant high blood pressure.[47] In randomized trials and meta-analyses, even though the risk of ischemic stroke was reduced, the risk of developing an hemorrhagic stroke was increased by using statins.[48] It has been estimated that there is an increased risk of 21% in the rate of this complication, which means an excess of 5–10 cases per 10,000

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patients treated for 5 years.[48] This risk is greater in patients with previous cerebrovascular disease and populations with a high risk of hemorrhagic stroke, like Asian people.

However, as with diabetes, the reduction in the rate of ischemic strokes clearly outweighs the increased risk of developing a hemorrhagic stroke.[48]

Other side effects

Although statins have been reported to increase serum levels of liver enzymes, statin administration is only rarely associated with serious liver injury. It has been estimated in post-marketing studies that the risk of liver injury may be around 1 case per 100,000 users.[49] However, its causal association with statins has not been proved yet. It is also important to consider that the "liver enzymes" aspartate aminotransferase and alanine aminotransferase are also present in skeletal muscle. Thus, muscle toxicity could lead to increased levels of "liver enzymes". Determination of creatine kinase and gamma-glutamyl transferase may be helpful to distinguish muscle from liver involvement in these patients, as creatine kinase elevation indicates muscle damage, while an increase in the gamma-glutamyl transferase is associated with liver damage.

Post-marketing reports of individuals with cognitive impairment that improved after statin withdrawal has suggested that statins may lead to memory loss.[50] In fact, since 2012 the FDA required to add cognitive side-effects to the drug label of all statins. However, large randomized trials and subsequent assessment of the FDA surveillance databases found similar rates of cognition-associated adverse events in patients taking and not taking statins.[50] Overall, it remains in question whether statins have any cognitive side effects.

Interestingly, even if an observational study analyzing the records of more than 2 million people suggested that statins may increase the risk of developing cataract,[51] later randomized clinical trials refuted this finding.[52] Moreover, there is no evidence that eye-related microvascular complications increase with statin therapy, despite the increased risk of diabetes.[53] Paradoxically, statin therapy has been suggested to reduce the progression of age-related macular degeneration, but, as with the negative visual side effects, this observation is not backed-up by the results of randomized trials.[54]

Considering the increased risk of diabetes in patients taking statins, it would be reasonable to consider whether these drugs to impact kidney function. However, randomized trials have reassuringly failed to prove any deleterious effect of statins on kidney function.[55,56]

Data regarding cancer risk associated with statin treatment is somewhat conflicting. A large database analysis showed a reduction in the rate of cancer mortality[57] but some clinical trials reported small increases in the incidence of breast cancer[58] and all-site cancer.[59] Of note, a meta-analysis on randomized clinical trials concluded that statin treatment was not associated with cancer at all.[60]

Finally, several other side effects have been attributed to statins, including quality of life, sleep disturbances, suicidal behaviors, neuropathy, erectile dysfunction of aggression, but, as many of the previous ones, these claims do not have enough supportive evidence backing them up.[16]

Conclusion

In conclusion, statins are highly effective drugs that have the ability to reduce the risk of major cardiovascular events up to 10% in primary prevention and 5% in secondary prevention over 5 years. However, about 0.5–1% patients over this same period of time may develop side effects, most of them mild. Nevertheless, given the great number of patients under statin treatment, these adverse effects will be common in clinical practice and thus, must be well-known by the medical community in order to be promptly diagnosed and correctly managed.

Conflict of interests

The authors declare no conflict of interests.

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