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Review Article

THE ADVANTAGES AND DISADVANTAGES OF STATIN THERAPY FOR DYSLIPIDEMIA

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Abstract

Background: More than three quarters of cases of atherosclerosis are directly caused by abnormalities in lipids profile, which is known as dyslipidemia. Atherosclerosis is considered one of the most causes leading to death around the world. the treatment of dyslipidemia is considered one of the important measures to decrease the risk of cardiovascular events. Effective use of statins leads to improvement in overall mortality and reduce the number of cardiovascular events up to 20%.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: statin, hyperlipidemia, advantages of statin therapy, disadvantages of statin therapy, adverse effects of statin therapy, dyslipidemia management

Aim: In this review, we aim to study the impact of dyslipidemia, understand statin therapy, and focus on its advantages and disadvantages.

Conclusion: Among all proposed therapies, the use of statins has been associated with best outcomes and highest efficacy. Statins have been found by most studies to achieve the best results in reducing the concentrations of LDL cholesterol and hence the risk of developing cardiovascular diseases. Statins have been tested and proven efficient on most subpopulations, with different efficacy related to each type of statins. In addition to their high efficacy, statins have a relatively safe profiles with no significant adverse events. The most common adverse events following the treatment of statins is the development of muscle pain or myopathy, which is most likely self-limited and recovers following the cessation of the disease. Other possible adverse events include diabetes mellitus type 2 and the development of hemorrhagic strokes.

Keywords: Dyslipidemia, Hyperlipidemia, Statin Therapy

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INTRODUCTION:

Atherosclerosis is considered one of the most causes leading to death around the world. It is associated with the development of several cardiovascular diseases like acute coronary syndrome, strokes and cerebrovascular events, and diseases of arteries. More than three quarters of cases of atherosclerosis are directly caused by abnormalities in lipids profile, which is known as dyslipidemia, along with cigarettes smoking and hypertension. Moreover, dyslipidemia and associated atherosclerosis are considered the strongest predisposing factors for the development of a myocardial infarction [1]. Therefore, the treatment of dyslipidemia is considered one of the important measures to decrease the risk of cardiovascular events. In fact, previous trials have found that the aggressive treatment with statins to decrease cholesterol levels is associated with high efficacy in significantly decreasing the development of cardiovascular events [2].

However, despite the use of statins and other approved agents for the treatment of dyslipidemia, rates of cardiovascular events remain to be relatively high making it necessary to conduct further studies to improve treatment and further decrease these events. Many studies have recently been targeting newer treatment approaches that aims at increasing the levels of HDL cholesterol and decreasing the levels of triglycerides, rather than just targeting LDL cholesterol. These new treatments may provide better efficacy in decreasing cardiovascular events especially in patients with diabetes, who generally have a bad prognosis of atherosclerosis [3].

METHODOLOGY:**• Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: statin, hyperlipidemia, advantages of statin therapy, disadvantages of statin therapy, adverse effects of statin therapy, dyslipidemia management

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

STATINS:

A clear strong correlation is present between the effective use of statins and the improvements in overall mortality and the number of cardiovascular events, which are reduced in about 20% following effective statins treatment that achieves 1.0 mmol/L decrease in the levels of LDL cholesterol. Moreover, the efficacy of statins is dose-dependent with higher efficacy achieved when patients receive more intensive treatment [2].

Studies have found that benefits of statins are more prominent in patients with coronary artery disease, cerebrovascular events, and diabetes mellitus. A recent meta-analysis has shown that the use of statins is also beneficial following acute myocardial infarctions treated with percutaneous procedures [4].

Based on the results of many large studies and meta-analyses, statins have a relatively safe profile with no serious adverse events, and no increase in the risk of developing cancers or death to non-vascular causes [2].

Common adverse events associated with the use of statins include myalgia, which is increasing among the patients who are using statins. Additionally, according to an observational study that included more than two million patients, the use of statins was associated with an extremely low incidence of developing acute renal failure, which can be dose-dependent.

In another study on over 1,700 patients who received high doses of statins for twelve weeks, only one hospital admission was observed [5]. Another meta-analysis concluded that diabetes mellitus type 2 may develop in one of each 255 patients treated with statins for more than two years [6].

Some studies claim that the long-term use of statins can lead to the development of cognition impairments. However, these claims are only based on small observational studies, and no solid evidence support them. therefore, larger studies must be conducted before reaching conclusions on this issue. The main question in the use of statins remains; when is the best time to initiate statins in a healthy individual? The answer to this question remains controversial and requires more larger studies to reach solid conclusions.

PROS OF STATINS:**Lipid lowering effect**

Cardiovascular disease is considered to be the

number one cause of death around the world, and hence is one of the most concerning health issues in most countries. In fact, reports suggest that cardiovascular diseases alone are responsible for the more than 17,000,000 deaths annually, which corresponds to 35% of deaths [7].

During the early 1900s, the discovery of cholesterol plaques was made. These plaques were found to be present in the coronary vessels of patients who suffered from fatal myocardial infarctions [8]. This period was associated with a significant increase in the risk of coronary heart disease and associated mortality, with lack of sufficient information on the pathogenicity and proper prevention and treatment of this disease [9]. In an attempt to establish predisposing factors that lead to the development of coronary heart disease, a large prospective cohort was conducted in Massachusetts in the year 1948. After this study, authors were able to conclude that the concentrations of LDL cholesterol were proportionally correlated with the development of coronary heart disease, and LDL cholesterol is the main factor leading to the development of the disease [10].

This led to attempts by researchers to prevent and treat coronary artery disease by targeting LDL cholesterol levels, and many studies were conducted to propose methods to achieve significant reductions in the levels of LDL. Studies found that the use of bypass surgery or following a diet with low cholesterol could improve LDL levels and thus decrease the rates of developing coronary artery disease and myocardial infarction. These reductions in risk were proportionally correlated with the magnitude of LDL reduction. However, these measures were not convenient for many reasons and could not achieve significant LDL reduction. Later, statins were introduced to become the best, most efficient drugs used to decrease the concentrations of LDL cholesterol [11].

Since the introduction of statins, most studies concluded that statins have higher efficacy in lowering LDL cholesterol concentrations than any other agent or procedure. Therefore, statins were associated with the best results when trying to decrease the risk of developing coronary artery diseases and cardiovascular events generally. A large meta-analysis studied the effects of statins in improving cardiovascular outcomes and preventing coronary artery disease in different subpopulations and found that beneficial effects of statins are significant in all ages, both sexes, all ranges of LDL baseline concentrations, diabetics or non-diabetics,

the presence of high blood pressure or normal blood pressure, the presence or absence of a history of acute coronary syndrome, and the presence or absence of other cardiovascular conditions [12].

Studies estimate that the risk of developing a major cardiovascular event can decrease by up to 22% for each one mmol/L decline in LDL cholesterol levels. Moreover, overall mortality and vascular-specific mortality can also decrease by 10% and 14%, respectively, for each one mmol/L decline in LDL cholesterol levels. For example, the use of 40 mg atorvastatin can lead to up to 50% reduction in LDL levels, which corresponds to about 2-3 mmol/L. Achieving and maintaining this reduction in LDL concentrations for five years will lead to the reduction of the risk of developing cardiovascular events by 10% in patients who already have a high risk of developing a cardiovascular or a cerebrovascular event, and by about 5% in individuals who are otherwise healthy and do not have a high risk of developing a cardiovascular or a cerebrovascular event [2].

Many pharmacological agents that belong to the statin's family are present, with each having different characteristics and efficacy. For example, simvastatin and pravastatin are both associated with weaker effects in decreasing LDL cholesterol levels; both can provide about 35% decrease when prescribed at 20 mg. On the other hand, rosuvastatin and atorvastatin, along with other new agents, are associated with higher efficacy that can reach 50% reduction of LDL concentrations when prescribed at 20 mg [13]. This efficacy of different agents depends mainly on the agent itself, and is not affected by the characteristic of the patient. Another important point is that for any given statin, the use of a double dose is associated with a 6% additional reduction of LDL concentrations [14].

In addition to achieving significant decline in the levels of LDL cholesterol, statins also prevent the development of cardiovascular events by decreasing the oxidation of LDL cholesterol, enhancing atheroma plaques stability, preventing the development of endothelial dysfunctions, inhibiting the proliferation of vascular smooth muscles, and decreasing the overall activity of platelets.

Pleiotropic effects

Atherosclerosis is a pathology that results from complicated mechanisms that include dysfunctions in the endothelial tissue, inflammatory reactions, and the formation of clots. As we previously mentioned, the use of statins is not only associated with

decreasing cholesterol levels, but also with other benefits. One important mechanism by which statins can improve atherosclerosis is by blocking the products of mevalonate. This is usually called the pleiotropic effect and is responsible for modulating almost all mechanisms involved in the development of atherosclerosis [15].

Improvement of endothelial function

The presence of endothelial dysfunctions is considered to be the first step during the development of atherosclerosis and later cardiovascular events. Endothelial dysfunction can result from increased blood pressure, cigarettes smoking, and high glucose levels, which will impact the vasodilatation of vessels by decreasing NO levels. Statins, on the other hand, act on several pathways to enhance the production and synthesis of NO leading to improved vasodilatation and endothelial function [16].

Anti-inflammatory effects

Following endothelial dysfunction that leads to damage, atherosclerotic plaques is formed which will later include inflammatory cells and reactions. Statins can prevent the development of these inflammatory reaction as they can decrease the rates of C-RP and interleukins production, leading to decreased inflammation and thus decreased risk of cardiovascular events occurrence [17].

A previous study has concluded that the use of pravastatin in patients with elevated C-RP and SAA levels was associated with improved outcomes and higher decrease in risk of developing cardiovascular events when compared to similar patients with normal levels of these markers [18]. This study confirms that statins do not only act by decreasing cholesterol levels, but by also preventing and blocking inflammatory processes. Interestingly, the use of atorvastatin and simvastatin can decrease concentrations of C-RP regardless of the presence of dyslipidemia [19]. This have raised questions on the ability the use statins in patients with chronic inflammations but without dyslipidemia.

Immunomodulatory effects

In addition to their effects in decreasing inflammatory processes, statins have also been suggested to decrease the immunological reactions in patients who have received cardiac transplantation or in patients with autoimmune disorders like systemic lupus erythematosus, rheumatoid arthritis, vasculitis, ankylosing spondylitis, and systemic sclerosis, along with other autoimmune diseases. The immunological effects of statins depend on several factors including

the presentation of antigens and the activation of T cells. In addition, several in vitro studies have concluded that statins can inhibit the proliferation of lymphocytes and natural killers [20].

Anti-thrombotic effect

The final step during the development of atherosclerosis is the disruption of endothelium with the formation of blood clots leading to obstructing the flow of blood. The formation of blood clots can be inhibited by statins by decreasing tissue factor expression and blocking the aggregation of platelets. This will significantly decrease thrombin formation. In addition, procoagulant factors activity has also been found to decrease in patients being treated with statins.

Statins do not also inhibit the formation of clots, but also can participate in the destruction of clots by reducing the levels of PAI-1 and enhancing the activity of fibrinolytic enzyme plasminogen [21]. During the JUPITER study, the anti-coagulant effects of statins were proven as the use of statins led to lower rates of developing venous thromboembolism [22]. Later, a meta-analysis of published trials concluded that patients who receive statins have a 40% lower risk of developing deep venous thrombosis and pulmonary embolism than patients who did not receive statins [23]. Evidence also suggests that when statins are administered in patients with anti-phospholipid syndrome they could significantly reduce their risk of developing thrombosis [24].

Cons of statins

Despite having these significant benefits especially for cardiovascular diseases and coronary heart disease, statins can still have risks of developing adverse events. The two most common adverse events associated with the use of statins are myopathy and diabetes mellitus type 2 (especially with long-term use). Some studies have suggested the presence of a risk of hemorrhagic strokes, but evidence on this issue is not solid. Other possible adverse events include loss of memory, impaired cognition, the formation of cataracts, the decreased renal functions. However, these later adverse events are rare with no solid evidence linking them to the use of statins.

Myopathy

It is confirmed that the use of statins can be associated with the development of myopathy, which is usually self-limited. This myopathy is thought to be a result of statins direct reactions in the muscle

tissue, or a result of autoimmune reactions that are caused by the formation of autoantibodies. The development of direct myopathy is relatively rare and is thought to occur in less than 20 patients per 10,000 patients-year. This type of myopathy is usually self-limiting with complete recovery following the cessation of statins therapy. It is also characterized by being dose-dependent with varying severity of the disease, which could manifest as simple muscle pain, or sometime rhabdomyolysis and acute renal failure [25].

Several studies have confirmed that patients on statins have a higher risk of developing muscle pain [26]. However, the absolute increase in developing muscle pain remains to be low, which suggests that muscle pain could be associated with statins but not caused by them. This point is of special importance in patients who develop muscle pain on statins but still have normal CK levels [25].

Statins-induced myopathy associated with increased CK level is considered rare, and has an incidence of only one per 10,000 patients-year. Moreover, the incidence of severely increased CK levels that lead to the development of rhabdomyolysis and renal failure is even less and reach two per 100,000 patients-year [25]. However, this incidence has been shown to significantly increase when statins are used in combinations with CYP450 inhibitors. Moreover, Asian patients have also been found to have a higher risk of developing more serious adverse events with the use of statins [27].

The development of autoimmune myopathy is also rare with an incidence that is about two per 100,000 patients-year [28]. Autoimmune myopathy generally causes weakness and necrosis of proximal muscles. Unfortunately, this type of statins-induced myopathy is not reversible and self-limited. It does not stop or improve following the cessation of statins therapy, and therefore, it will definitely require treatment with immunosuppressive agents. In some rare cases, autoimmune myopathy has been reported in patients who have never been exposed to statins therapy [29].

Diabetes

Several large trials have found a significant associated between the use of statins and the development of diabetes mellitus type 2. The increase in diabetes risk in patients on statins appears to be dose-dependent and is also affected by the presence of other predisposing factors to diabetes like high BMI, glucose intolerance, or high HbA1c levels [6].

The pathophysiological mechanisms by which statins increase the risk of developing diabetes are not well-understood. Some authors have suggested that the decline of LDL concentrations caused by statins can increase the number of available LDL receptors, which can lead to pancreatic cells damage. However, no solid theory is present to explain this issue. Despite this increase in diabetes risk, the benefits of statins in decreasing the risks of cardiovascular diseases outweigh all the risks [30].

Hemorrhagic stroke

Many large cohort studies have suggested that the use of statins can increase the risk of developing cerebrovascular events and hemorrhagic strokes. Higher levels of LDL cholesterol are generally associated with lower risk of developing hemorrhagic strokes, especially in patients who have hypertension [31]. Therefore, the use of statins is supposed to increase the risk of developing a hemorrhagic stroke by decreasing the concentrations of LDL in the blood. Previous trials have been able to conclude that the risk of developing an ischemic stroke is significantly decreased in patients who use statins. However, the risk of developing a hemorrhagic stroke might be increased [32].

Some studies estimate that the use of statins is associated with a 20% increase in the risk of developing hemorrhagic strokes, which corresponds to the absolute increase of about 10 cases per 10,000 patients-year, when statins are used for five years. Asian patients and patients who have a history of previous cerebrovascular events have a higher risk of developing a hemorrhagic stroke when they are on statins therapy. Despite the presence of evidence on the increased risks of hemorrhagic strokes with statin therapy, the benefits of statins use still outweigh the risks [32].

CONCLUSION:

Dyslipidemia is considered one of the most serious conditions that is associated with many morbidity and late complications. Dyslipidemia is significantly associated with the later development of atherosclerosis, coronary artery disease, along with other cardiovascular diseases, leading to a significant increase in the mortality of patients. Therefore, in order to prevent and treat these cardiovascular diseases, dyslipidemia must be sufficiently addressed and treated to eventually decrease overall and cardiovascular specific mortality. Many studies have been conducted to establish best methods to decrease LDL cholesterol levels and thus decrease the incidence of cardiovascular events. Among all

proposed therapies, the use of statins has been associated with best outcomes and highest efficacy. Statins have been found by most studies to achieve the best results in reducing the concentrations of LDL cholesterol and hence the risk of developing cardiovascular diseases. Statins have been tested and proven efficient on most subpopulations, with different efficacy related to each type of statins. In addition to their high efficacy, statins have a relatively safe profiles with no significant adverse events. The most common adverse events following the treatment of statins is the development of muscle pain or myopathy, which is most likely self-limited and recovers following the cessation of the disease. Other possible adverse events include diabetes mellitus type 2 and the development of hemorrhagic strokes.

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