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MERITS AND DEMERITS OF STATINS, A CHOLESTEROL LOWERING AGENT-A REVIEW

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ABSTRACT

Background: Statins are themselves the most common class of drugs may be synthetic in origin or derived from microorganisms used to treat hypercholesterolemia. An increasing number of patients are turning to and using statins as to combat hypercholesterolemia. However, a comprehensive and objective examination of the merits and demerits of said use is required as to properly guide physicians and patients.

Main body: In order to accomplish this, a number of published journals were examined in order to gather information and insight into the matter. Based on the results it was noted that statins actively reduce cholesterol (LDLc and total cholesterol) and apolipoprotein B levels and prevent the risk of cardiovascular diseases. However, it was also presented that statins can be linked to a number of adverse effects including but not limited to muscle complications, rhabdomyolysis and pancreatitis.

Conclusions: At present the number of viable merits as it pertains to statin use as a means of controlling or treating hypercholesterolemia are numerous and includes but is not limited to: increased HDL cholesterol and Apolipoprotein A1 as well as a noteworthy decreased in total cholesterol. Further research be done in order to expand further upon the uses and possible adverse effects of statins

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INTRODUCTION

Statins are themselves the most common class of drugs may be synthetic in origin or derived from microorganisms (Quintao, 1994) used to treat hypercholesterolemia. The hypercholesterolemia is commonly defined as the occurrence wherein there is too much cholesterol within the body which in turn increases the risk of heart disease and stroke (Anderson, 2007). This in itself is listed as the leading cause of preventable death worldwide, especially within first world and developing countries (Institute of Medicine, 2010 and Barter, 2014). In order to treat the aforementioned condition, an increasing number of patients are turning to statin use (Quintao, 1994). The mode of action of statins involves the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (Marcoff, 2007).

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Via this, the liver can no longer access HMG CoA reductase as to make cholesterol. With this action in place, the body then presents with a reduced amount of LDL cholesterol and triglycerides circulating throughout the body whilst simultaneously increasing the amounts of HDL cholesterol (http://www.heart.org/HEARTORG/Conditions/Cholesterol/PreventionTreatmentofHighCholesterol/Cholesterol-Medications_UCM_305632_Article.jsp#.WNHnARLyu34.). With the increase in patient use as well as the relative effectiveness of the drug in question, a number of studies have been done to validate and examine the related effects of statin use as it pertains to hypercholesterolemia. This in turn has led to the establishment and continual update of the American College of Cardiology and American Heart Association guidelines (Lloyd-Jones, 2017 and http://www.aafp.org/afp/2014/0815/p260.html). Herein the intensity and risks of statin use is clearly stipulated as a means to reducing the risk of Atherosclerotic Cardiovascular Disease.

Main Text

A number of studies have looked into the effectiveness of statins as a means to combat hypercholesterolemia. A study done by Avis et al in 2007 sought to examine the effectiveness of statin use in treating children who presented with heterozygous familial hypercholesterolemia (HeFH) (Avis, 2007 and Avis, 2013). Herein the researcher studied children age 8 to 18 who presented with HeFH. It was noted that with a statin treatment, the patients in question had a significant reduction in total and LDL cholesterol as well as apolipoprotein B. A notable increase in HDL cholesterol as well as apolipoprotein A1 were also noted. Furthermore, the study was done under a double blind setting and when considering the adverse effects, no statistically significant differences were noted between treatment and placebo groups. This in itself advocates for the efficiency of statin use to treat hypocholesterolemia. The British Medical Journal published an article in 2014 expanded upon the implications and effectiveness of statin use (Godlee, 2014). Herein it was noted that statins are useful for secondary prevention, such as with patients who suffered myocardial infarction (Godlee, 2014). However the author went on to elaborate that statins have unclear and doubtful benefits as it relates to primary prevention. The patients under consideration were those who did not have any preexisting cardiovascular problems but rather presented with other risk factors such as high cholesterol, being diabetic or smokers and others. It was also noted that statins present with additional benefits to patients who present with high cardiovascular risks. However there is no clear consensus on what defines the intensity of such risks or the benefits reported (Godlee, 2014).

Another study published by the BMJ examined the effects of statins on primary prevention and it was concluded that there was no clear or significant benefit to patients who presented with low cardiovascular risk (that is- with a less than twenty percent risk at 10 years) (Deckers, 2011). Thus far it can be noted that there are quite mixed reviews on statin use. However the most worrying concern should be that of adverse side effects. That is- if the potential adverse effects of statin use can be mitigated or outnumbered by the positive outcomes. The most commonly recognized and reported adverse effect of statin use, according to both the American Journal of Cardiovascular Drugs as well as the BMJ, is that of muscle complications (Godlee, 2014 and Beatrice, 2008). This entails muscle pain, fatigue, myositis and myalgia. However it must be added that statins often serve to decrease muscular pain, especially in cases of chronic peripheral arterial disease (Deckers, 2011). Furthermore, statin use has been noted to present with exercise-induced muscle pain and increased oxidative stress (Bouitbir, 2011). To this effect, professional athletes with familial hyperlipidemia rarely use or are able to tolerate statins owing to the posited adverse effect. Combined statins and beta blockers adversely affect perceived effort and cardiorespiratory function (Beatrice, 2008). Furthermore, athletes and body builders would be deterred from statin use owing to its down regulation of the ubiquitin proteasome pathway, which in turn results in slower muscle growth (Urso, 2005). It must also be noted that statin use has also held some reports of rhabdomyolysis (Beatrice, 2008). This in itself is classified as a severe skeletal muscle breakdown resulting in muscle contents leaking into circulation (https://www.ncbi.nlm.nih.gov/pubmed/11898964). However the linkage between statin use and rhabdomyolysis was found to be more commonly reported when other drugs were used which increased the effects of the statin (Mendes, 2014 and Deslypere, 1991). With respect to the above, the statin which was most commonly reported to be linked to rhabdomyolysis was simvastatin wherein patients were commonly prescribed a dosage of 40mg/day (Mendes, 2014). Following this was atorvastatin with a prescribed dosage of 10mg/day (Mendes, 2014). On the lower end of the spectrum were cerivastatin, lovastatin, rosuvastatin, pravastatin and then fluvastatin. In addition to what has been presented thus far, statin use can also present with some minor effects such as headaches, diarrhea, stomach discomfort and rashes (Leuschen, 2013 and Maji, 2013). These occur frequently but are themselves self-limiting with continued statin use. Following the above, there are some infrequent adverse side effects to statin use. These include dermatomyositis, polymyositis and inflammatory myopathies which are the result of the pro-oxidant effects of statins (Beltowski, 2005 and Koslik, 2017). The aforementioned effect of statins predominate in some patients and can then lead to pro-inflammatory effects. This is a cause of concern as statins reduce the LDL-c transport and/or production of key anti-inflammatory nutrients such as coenzyme Q10, retinol and cholecalciferol. However other studies have noted that statins present with anti-inflammatory properties and this in turn makes them clinically important as it pertains to lowering cardiovascular risks (Quist-Paulsen, 2010). Additional adverse effects include Myasthenia Gravis (MG) (Oh, 2008), Rippling Muscle Disease (RMD) (Baker, 2006) and Guillain-Barré Syndrome (Collidge, 2010). With respect to MG, muscle weakness resulting from statin use can exacerbate any existing MG conditions or emulate other related conditions[13]. In this regard, drug interactions with dual mitochondrial toxicity may further progress MG symptoms.

Statins have also presented with some rare cases of bilateral muscle weakness in tandem with dysphagia, dysarthria and dyspnea (Beatrice, 2008; Edholm, 2010 and Ravnskov, 2010). However, with these instances, progression continued even after statin discontinuation with an eventual culmination in death (Beatrice, 2008). Pancreatitis also presents as a rare adverse effect of statin therapy (Singh, 2006). The mechanism by which statin induced pancreatitis occurs may be one of the following three: an immune-mediated inflammatory response, direct cellular toxicity and metabolic effect (Etienne, 2014). Additionally a case of multiple organ toxicity, including acute pancreatitis, which was due to the interaction between lovastatin and erythromyc in was noted (Etienne, 2014). Further research presented a case of acute pancreatitis with rhabdomyolysis due to the interaction between lovastatin and gemfibrozil (Etienne, 2014). Acute pancreatitis was also reported in the context of interaction between simvastatin and fenofibrate. Interestingly, with regards to combined simvastatin and fenofibrate therapy.

Furthermore, statins have been linked to some cognitive issues such as memory loss (Wagstaff, 2003) or confusion as noted by the FDA. However these effects tend to reverse or cease once the patient ceases statin use. In addition to the previously mentioned risks, there is also the concern of statin use being linked to increased incidence of diabetes amongst its users (Sattar, 2010 and doi:10.1007/s00125-015-3528-5). These risks are more associated with intensive-dose therapies however and as such treatment with statins should be initiated at lower dosages. Furthermore, high dose statins are best avoided in elderly and high risk patients.

Table 1. Merits and Demerits of Statin Use

Statins	Merits	Demerits
Atorvastatin (Lipitor)	Decreases LDL cholesterol and Apolipoprotein B	Unclear primary prevention benefits
	Increases in HDLs and Apolipoprotein A1	Muscle complications such as myositis and
Fuvastatin (Lescol)	Decreases total cholesterol	myalgia
	Possibly decreases symptoms of anxiety and depression	Down regulation of ubiquitin proteasome
Lovastatin (Altoprev)		Concern of increased incidence of diabetes
Pitavastatin (Livalo)	Significantly reduces risk of all-cause mortality in cardiovascular patients	Fever
	Works better than any other cholesterol treatment	Rashes and head ache
Pravastatin (Pravachol)		Bilateral muscle weakness
	Stabilizes the blood vessel lining, which benefits the whole body	Memory loss and confusion
Rosuvastatin (Crestor)	Makes plaque less likely to rupture in the heart, lowering the risk of a heart attack	
Simvastatin (Zocor)	Helps to relax the blood vessels, which leads to a decrease in blood pressure	

It must also be added however, that even though not proven, pravastatin seems to reduce the risk for Non-Obese Diabetes (NOD) (Aiman, 2014). However even with the adverse effects noted above, a number of studies have been emerging to either dispute or present new plausible methods to mitigate these actions. It must also be noted that new research into cholesterol-lowering statin drugs and serotonin-1A receptors may explain the relationships between cholesterol levels and symptoms of anxiety and depression. Furthermore, a study done in 2009 by Brugts et al posited that statin use significantly reduced the risk of all-cause mortality amongst cardiovascular and diabetes patients[35]. These results were further emphasized by Spannella et al in 2017 wherein it was noted that statins in tandem with ACE inhibitors presented with notable benefits to the cardiovascular system of patients (Spannella, 2017). What is extremely noteworthy is that within this study, the patients had an average age of over 88 years wherein established scientific evidence is still lacking. It can be argued that the merits of statin use in patients with cardiovascular issues are not as prominent due to patients failing to comply with the therapy in question. A study done by Soška and Kyselák in 2017 focused on this[37] and noted the clear benefits. However the long term compliance of patients to the therapy was extremely low. The withdrawal from the treatment resulted in the increased expressions of statin side effects such as muscular issues and increased creatine kinase. The findings presented thus far can be summated into the following table for ease of understanding and comparison.

Despite the benefits of statin use, especially as it pertains to cardiovascular treatments, the challenges and risks are perceived to be too much for some. In this regard studies have been initiated into alternative methods. One such method is of proproteinconvertasesubtilisin-kexin type 9 (PCSK9) inhibitors. Hess et al are currently reviewing said drug class in tandem to statins as a means of controlling and/or treating hyperlipidemia (Spannella, 2017). Fischer and Julius have also undertaken a study to observe effectiveness of PCSK9 inhibitors within a patient who has presented with statin intolerance as it pertains to controlling cardiovascular disease (Fischer, 2017). Giugliano et al recently published their findings on the use of the PCSK9 inhibitor Evolocumab in high risk patients who were already receiving statins (Giugliano, 2017). Herein it was noted that the drug in question was effective in reducing cardiovascular events in patients who presented with cardiovascular disease. This occurred regardless of potency of background statin potency or LDL-C baseline. Shrivastava and colleagues have also explored the effect of chronic cholesterol depletion induced by mevastatin on the function and dynamics of the human serotonin-1A receptors stably expressed in animal cells. Their results showed a significant reduction in the level of specific ligand binding and G-protein coupling to serotonin-1A receptors upon chronic cholesterol depletion, although the membrane receptor level is not reduced at all. The effect of chronic cholesterol depletion on the ligand binding of serotonin-1A receptors is reversible. In addition, the researchers found novel changes in receptor dynamics with chronic cholesterol depletion. These results have broad implications in light of recent reports of anxiety and depression in patients receiving long-term statin therapy.

Conclusion

At present the number of viable merits as it pertains to statin use as a means of controlling or treating hypercholesterolemia are numerous and includes but is not limited to: increased HDL and Apolipoprotein A1 as well as a noteworthy decreased in total cholesterol. However there is still room for future research and potential drug development and improvements.

Declarations

Ethics approval and consent to participate:Not applicable because this is a review article

Consent for publication: Not applicable

Availability of data and material: All cited and reviewed articles are listed in the proceeding references section.

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