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An Overview on the Role of Statins in Dyslipidemia Management in Primary Health Care

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ABSTRACT

An imbalance of cholesterol serum concentrations characterizes dyslipidemia. It can cause plaque formation in the arteries, increasing the chance of atherosclerotic cardiovascular illness events, such as stroke or coronary artery disease. In individuals with mixed dyslipidemia and primary hypercholesterolemia without reaction to exercise, diet, or different non-pharmacological treatments, all statins were suggested. They have shown positive outcomes in preventing cardiovascular events risk in such patients. To review the risk factors of dyslipidemia and the role of statins in treating such a disease in the recent literature. Articles were selected by the PubMed database, and these keys were utilized in the Mesh (("Dyslipidemia" [Mesh]) AND ("Statins"[Mesh]) OR ("management" [Mesh])). Statins have been shown to lower major non-fatal atherothrombotic events and cardiovascular mortality in various groups' primary and secondary preventive studies. Therefore, they are recommended for individuals with established heart disease, diabetes mellitus, an LDL above 190 mg/dL, and those with a 7.5% or greater 10-year risk of cardiovascular events.

Keywords: *Statins, Dyslipidemia, Primary health care, Management*

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INTRODUCTION

Dyslipidemia is characterized by cholesterol serum concentrations imbalance, including high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL). The quantity of cholesterol in the body is adjusted by LDL and HDL, and an imbalance might raise the cardiovascular accidents hazards such as stroke and myocardial infarction. In hypertriglyceridemia and mixed dyslipidemia, high triglyceride and cholesterol contents are two other varieties of dyslipidemia. Increased LDL levels can cause plaque formation in the arteries, increasing the probability of atherosclerotic cardiovascular diseases (ASCVD), such as stroke or coronary artery disease. Increased HDL levels (60 mg/dL) can reduce the ASCVD risk because HDL removes cholesterol from the circulation (Cooney *et al*., 2009).

More than 100,000,000 individuals, or about 53%, have high LDL contents in the United States. In spite of this, just about 50% of people with high LDL receive therapy to decrease their contents, and approximately one-third of the individuals who receive treatment attain adequate control. Furthermore, about 31 million individuals in the United States have total cholesterol contents above 240 mg/dL, putting them at nearly double the hazard of ASCVD as those with total cholesterol contents within the target range (CDC, 2011; Mozaffarian *et al*., 2016).

All statins are recommended in individuals with mixed dyslipidemia and primary hypercholesterolemia without any reaction to exercise, diet, or different non-pharmacological treatments. They have shown positive outcomes in preventing cardiovascular events risk in such patients. Therefore, we aim

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in this article to review the role of statins in treating dyslipidemia.

MATERIALS AND METHODS

Articles were selected using the PubMed database, and the following keys were utilized in the Mesh ((“Dyslipidemia” [Mesh]) AND (“Statins”[Mesh]) OR (“management” [Mesh])).
Regarding the inclusion criteria, the articles were chosen according to the following topics: Statins and dyslipidemia management.
All other papers without one of these topics as their primary endpoint were the exclusion criteria.
About 60 publications were selected as the most clinically related ones out of 2,923 papers indexed in the last decade, and their full texts were investigated. Totally 20 of the 60 were included after a comprehensive evaluation. Additional publications and research were found using reference lists from the linked and recognized studies. To help practicing physicians assess cirrhosis most practically and simply, expert consensus commentary and recommendations were added .

RESULTS AND DISCUSSION

Dyslipidemia risk factors
A higher risk of dyslipidemia is linked to several variables. Physical inactivity, smoking, obesity, and a diet rich in trans or saturated fats, are all modifiable risk factors. Diseases including chronic renal disease, biliary obstruction, type 2 diabetes mellitus, hypothyroidism, and hypertension, are secondary causes of increased LDL (Mozaffarian *et al*., 2016). Diuretics, cyclosporine, and glucocorticoids are examples of medications that can raise LDL levels (Stone *et al*., 2004). Data on the involvement of gender and race in the formation of dyslipidemia has been contradictory; nevertheless, some risk factors, such as obesity among non-Hispanic blacks, may be more frequent in specific races, leading to a higher prevalence of dyslipidemia in that group (Ogden *et al*., 2004).
The development of high cholesterol (Total cholesterol contents above 320 mg/dL) in the form of familial hypercholesterolemia (FH) can also be influenced by genetics. FH is an autosomal dominant trait that causes substantial LDL and total cholesterol increases from birth and early ASCVD (Vogt, 2015; Krähenbühl *et al*., 2016). Genetic mutations cause FH in the LDL receptor (LDLR), which reduces LDL metabolism, or genetic mutations in the apolipoprotein (apo) B gene, that decreases LDL particle binding to the LDLR to DNA testing. Most people with FH have a mutation in the LDLR gene (Nordestgaard *et al*., 2013; Khera *et al*., 2016). When there are insufficient functioning LDLRs, the amount of cleared LDL decreases, increasing circulating LDL. People with FH have a higher chance of developing coronary heart disease than patients without FH. Although FH frequency did not differ by gender, it differed by ethnic group, with whites, blacks, and other Hispanics having the highest prevalence and Mexican Americans having the lowest. The two types of FH are homozygous (HoFH) and heterozygous FH (HeFH). HeFH is more frequent in the United States, affecting around 1 in 500 persons, and is linked to LDL values of 200 to 450 mg/dL (Vishwanath & Hemphill, 2014). HeFH patients are more likely to develop coronary artery disease before they reach the age of 60 (Nordestgaard *et al*., 2013). HoFH is a rarer form of the disease, affecting around 1 in 300,000 to 1,000,000 persons, although it is linked to considerably higher LDL values (450 to >1000 mg/dL) than HeFH (Vishwanath & Hemphill, 2014; Vogt, 2015). Patients with HoFH who are not treated may die before they reach the age of 20 (Nordestgaard *et al*., 2013).

Statins and their role in dyslipidemia
Statins decrease levels of cholesterol via three interconnected processes (Zodda *et al*., 2018). The first is the suppression of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that slows down the conversion of HMG-CoA to mevalonic acid, a precursor to sterols like cholesterol. Although inhibiting this enzyme lowers liver cholesterol, compensatory processes increase HMG-CoA reductase and LDL receptors. Statins work by an indirect mechanism in the latter scenario, boosting receptor-mediated absorption of LDL and therefore lowering plasma LDL. They also diminish VLDL and intermediate-density lipoproteins, which are LDL precursors, owing to the growing number of receptors: this third mode of action helps lower plasma LDL. Atorvastatin and rosuvastatin, in particular, cause a significant reduction in plasma triglycerides by removing greater quantities of triglyceride-rich VLDL (Stender *et al*., 2005; Zodda *et al*., 2018).
Statins, the structural mimics of the HMG-CoA intermediate, generated during mevalonate synthesis by HMG-CoA reductase. Only simvastatin and lovastatin are inactive lactones hydrolyzed into the active Beta-hydroxy acid form in the body (Tiwari & Khokhar, 2014). Because of the substantial first-pass impact, all statins have a very poor systemic bioavailability. Unlike other statins, lovastatin and simvastatin are administered as inactive lactone prodrugs. The content of active and inactive metabolites and the degree of metabolism are the primary differences between statins. Because all statins include active metabolites, their effectiveness is influenced by the profile of the active metabolites and the parent drug. When compared to other statins (>90%), rosuvastatin and atorvastatin have the greatest terminal half-lives (11–20 h), pravastatin has the lowest protein-binding (about 50%); moreover, statins have a short half-life (1–4 h) (Gazzerro *et al*., 2012).
All statins are suggested for those with mixed dyslipidemia and primary hypercholesterolemia who do not react to exercise, diet, or different non-pharmacological therapies. While lovastatin, pravastatin, and fluvastatin do not lower LDL contents in homozygous familial hypercholesterolemia who cannot produce rosuvastatin, simvastatin, LDL receptors, and atorvastatin do, owing to their ability to drastically reduce LDL cholesterol production in the liver (Marais *et al*., 2008). Any statin can be combined with other cardioprotective medications to reduce other risk factors in cardiovascular disease prevention (Wang *et al*., 2016).
The recommended dosage for hypercholesterolemia is 10–20 mg/day given as a single dose in the evening; patients who need a significant decrease in LDL (more than 45%) can start with 20–40 mg/day given as a single dose in the evening. At a dose of 5–10 mg/day, only rosuvastatin should be started, with maximal doses of up to 40 mg/day reserved for patients who have not met their treatment objectives at the lowest doses (Stender *et al*., 2005). The recommended dose for homozygous familial hypercholesterolemia is 40 mg daily in the evening. The typical dose for cardiovascular prevention is 20 to 40 mg/day,

given in a single dose at night, but the common dose for atorvastatin is 10 mg/day, that can be increased as required (Wang *et al*., 2016; Zodda *et al*., 2018).

LDL control

The Scandinavian Simvastatin Survival Study, published in 1994, demonstrated the value of statins in individuals with known vascular disease (Armitage *et al*., 2010; CTT, 2010). The active therapy group had a mean LDL level of 120 mg/dL. More studies confirmed the advantages of statins and lowering LDL levels from the high 120s to under 100 mg/dL. The Atorvastatin or Pravastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial found that treating patients with known risk with statins reduced their risk even more; the mean LDL content achieved in the group randomized to an intensive atorvastatin 80 mg per day regimen was 62 mg/dL (CTT, 2010; Mansi *et al*., 2013).

Also, new guidelines were released by the National Cholesterol Education Program's Adult Treatment Panel III, that included an optional target of LDL less than 70 mg/dL for individuals at extremely high risk. In 2008, the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) found a significantly lower incidence of major cardiovascular events after treatment with rosuvastatin 20 mg daily, with an achieved median LDL of 55 mg/dL, in seemingly healthy women and men with baseline LDLC levels of less than 130 mg/dL (Sattar *et al*., 2010; Dixon *et al*., 2014). Clinical research shows that lowering LDL by 39 mg/dL reduces the risk of cardiovascular events by 20% to 25%. Extrapolating the findings, lowering LDL below 40 mg/dL would reduce the risk of cardiovascular disease to zero. It was previously proved that a plasma content of LDL of just 25 mg/dL would be enough to provide cholesterol to cells (Kazi *et al*., 2016).

Cells can manufacture all of the cholesterol they require, implying that LDL is just a byproduct of the liver's removal of cholesterol from circulation. Non-Western populations provide additional evidence that reduced LDL has no negative consequences. In Native American and African tribal communities, total cholesterol levels are low at 100s mg/dL, with LDL values ranging from 50 to 75 mg/dL. Even lower amounts can be seen in elephants, baboons, and foxes. According to clinical study data, LDL levels below the current "normal" are also better (Clebak & Dambro, 2020).

The Cholesterol Therapy Trialists' Collaboration (CTT) examined data from over 160,000 individuals in 26 studies that compared more intense statin regimens to less aggressive statin regimens or statin treatment to no treatment. There was no point at which additional LDL reduction was not beneficial. Patients with an LDL content of less than 77 mg/dL who lowered their LDL to 50 mg/dL had a similar risk reduction of major vascular events as those with greater levels which decreased their LDL by the same proportion. In the JUPITER trial, even those with a baseline LDL of less than 60 mg/dL benefitted from statin therapy (CTT, 2010; Clebak & Dambro, 2020).

In conclusion, according to the 2013 ACC/AHA guidelines, statins are recommended for individuals with established heart disease, an LDL of more than 190 mg/dL, diabetics, and those who have a 7.5% or greater 10-year risk of cardiovascular events (Stone *et al*., 2014). The US Preventive Services Task Force advised statins for people aged 40 to 75 who have at least one risk factor and an estimated 10-year cardiovascular disease risk of 10% in 2016 (Clebak & Dambro, 2020).

Statin adverse effects

Musculoskeletal manifestation

Patients on statin treatment frequently complain of muscle aches and pains in the outpatient environment. The myopathy risk was determined to be 0.5 per 1000 patients over five years in the CTT meta-analysis, equivalent to a Number Needed to Harm (NNH) of 2000 (CTT, 2010). At every 4-6 months follow-up in the major randomized controlled Heart Protection Study, subjects were questioned explicitly about unexplained or new muscular discomfort or weakness. 6% to 7% of individuals experienced these symptoms at each follow-up visit, although there were no significant differences between those taking placebo and those on simvastatin. 32.9% of those on simvastatin and 33.2% of those taking placebo felt muscular discomfort at least once at the end of the trial.

In the SEARCH study, myopathy was uncommon during statin therapy. Patients on simvastatin 80 mg daily had a 0.9% chance of having a creatine kinase content greater than ten times the upper limit of normal. In contrast, those taking simvastatin 20 mg daily had a 0.03% (Armitage *et al*., 2010). However, creatine kinase levels should not be monitored regularly.

According to a national database, the incidence of muscular complaints reported in outpatient settings seems to be greater than in clinical trials, ranging from 9% to 20%. It was also shown that statin users have a 50% higher rate of muscular soreness than non-users. Statin users are also 50% to 60% more likely to experience musculoskeletal discomfort in the lower back and lower limbs. This increase in muscular discomfort is 100 times larger in absolute terms than documented in clinical studies (Mansi *et al*., 2013).

Liver Injury

There has been increasing evidence of statin-induced liver injury's low incidence. The Federal Drug Administration (FDA) has updated the mandatory product labeling for statins. Between 2000 and 2009, the FDA performed numerous post-marketing evaluations of hepatotoxicity and statins. In such evaluations, it was repeatedly observed that significant statin-associated liver damage was seldom reported, with a rate of 2 per million patient-years. Based on this information, the FDA no longer advises regular periodic monitoring of serum alanine aminotransferase (ALT) (Clebak & Dambro, 2020).

Diabetes risk

A meta-analysis of 13 statin studies, including 91,140 people, revealed that statin medication was linked to a 9% higher risk of developing diabetes. According to data analysis, the risk of developing diabetes with statins was highest in trials with older individuals. Still, neither changes in LDL concentrations nor baseline BMI explained the variance in risk. The number required to cause damage over four years of statin medication was discovered to be 255. The authors found that statin medication is related to a small enhanced chance of acquiring diabetes; nevertheless, the risk is minimal, and therapeutic management in individuals with moderate or high cardiovascular risk should not alter. This little possible diabetes risk and the considerable benefit of lowering cardiovascular

events must be discussed with patients and used to guide shared decision-making in clinical practice (Sattar *et al*., 2010).

Statins competition

Clinical studies have shown several pharmacological therapies to decrease the frequency of future atherothrombotic events in survivors of a previous episode in recent decades (Zodda *et al*., 2018). Particularly, statins have been shown to lower major non-fatal atherothrombotic events and cardiovascular mortality in primary and secondary preventive studies in various groups. These therapies are recommended by American and European standards and must be given to all individuals with a cardiovascular event and do not have any contraindications. On the other hand, the cost-effectiveness argument for anti-PCSK9 monoclonal antibodies is only getting started as an alternative to statins. Although it is possible to obtain a significant therapeutic goal with these drugs, given the high costs of a new treatment in the US (between $14,100 and $14,600 per year), some concerns have arisen about the vast potential of users, particularly when compared to traditional statin therapy ($100–180 per year). Because a year, for example, of therapy with mipomersen and lomitapide costs more than $170,000 and $270,000, respectively, costs and concerns about tolerability will continue to be limiting considerations for these two medicines (Kazi *et al*., 2016; Clebak, & Dambro, 2020).

CONCLUSION

Statins have been shown to major non-fatal atherothrombotic events and lower cardiovascular mortality in primary and secondary preventive studies in various groups. Therefore, they are recommended for individuals with established heart disease, an LDL of more than 190 mg/dL, diabetics, and those with a 7.5% or greater 10-year possibility of cardiovascular events.

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