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PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.2562883>Available online at: <http://www.iajps.com>**Review Article****ADHERENCE TO STATINS: A REVIEW****Haya Saad Alshaibani¹, Sarah Matrouk Alruwaily²**^{1,2} Medical Intern, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.**Abstract:**

Background Statins are medications that lower LDL-cholesterol levels. Discovered in 1971. Statins work by inhibiting Hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which is an enzyme that catalyses the reduction of HMG-CoA to mevalonate. Inhibition of this enzyme decreases cholesterol synthesis, leading to upregulation of LDL receptors in the liver. This increases LDL uptake by hepatocytes, which causes a decrease of LDL levels in the blood. The use of statins has several indications. Based on the American College of Cardiology /American Heart Association 2018 guidelines, the use of statins for dyslipidemia is recommended as a primary and secondary prevention of ASCVD (Atherosclerotic Cardiovascular Disease). Other FDA approved indications of statin use are stroke and myocardial infarction prophylaxis. *Purpose* The purpose of this review is to illustrate the factors affecting statin adherence, reasons of non adherence, and the potential interventions to improve adherence to these medications. *Methods* A PubMed search was used, with statin and adherence as keywords. Studies reporting factors affecting adherence to statins, reasons for non-adherence to them and interventions to improve adherence to statins were included in the review. *Results* Two articles illustrated the factors affecting adherence and one article listed reasons for non-adherence. Six studies suggested possible interventions to improve adherence. *Conclusions* Many factors may affect the adherence to statin in a positive or negative way. Full insurance coverage, Frequent follow up and lipid testing showed a positive impact on adherence. By knowing this, better counseling and planning upon starting therapy is advised. Frequent counseling sessions by pharmacist or physician may improve adherence to statins. Comprehensive information given to statins users increases their adherence and the success of reaching the target LDL levels. Interventions such as cardiovascular risk counseling, educational pamphlet, adherence report or reminders mailed to the patients during therapy period may also increase adherence rate.

Keywords: Adherence, statin, compliance, LDL, and Cholesterol.**Corresponding author:****Haya Saad Alshaibani,**Email: alshaibani.h@gmail.com**QR code**

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INTRODUCTION:

Statins were discovered in 1971 by Akira Endo, a Japanese chemist (1). Currently there are several statins in the market, like Atorvastatin, Rosuvastatin and Simvastatin. Statins lower the level of Low density lipoprotein (LDL) which has the function of transporting cholesterol throughout the body. They work by inhibiting Hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which is an enzyme that catalyses the reduction of HMG-CoA to mevalonate. This reduction is an important step in the cholesterol synthesis pathway. So Inhibition of HMG CoA reductase decreases cholesterol synthesis, and lowers hepatic cholesterol concentrations. This also leads to upregulation of LDL receptors in the liver. This increases LDL uptake by hepatocytes, which causes a decrease of LDL levels in the blood (2). Statins have several indications. Based on the American College of Cardiology /American Heart Association 2018 guidelines, the use of statins for dyslipidemia is recommended as a primary prevention of ASCVD (Atherosclerotic Cardiovascular Disease) for non-diabetic patients aged 40-75 years with LDL-C level $\geq 190\text{mg/dl}$, and diabetic patients with LDL-C level of 70-189 mg/dl. It is also recommended to use statins as a secondary prevention of ASCVD in patient aged 18 years and above. Other FDA approved indications of statin use are stroke and myocardial infarction prophylaxis. The main side effect of statin use is myopathy which is a dose dependent effect. The most serious reaction is rhabdomyolysis, which is rarer. Hepatotoxicity and elevated liver enzymes can be observed with the use of statins and may be transient (3). The aim of this review is to illustrate the factors affecting statin adherence, reasons of non adherence, and the potential interventions to improve adherence to these medications.

METHODS:

A PubMed search was conducted using the keywords: statin AND adherence in the title of clinical trials and observational studies only. The search yielded a total of 21 articles. Nine articles are included in this review. The reason for exclusion of other articles was that they did not match the aim of this review.

RESULTS AND DISCUSSION:

Two articles illustrated the factors affecting adherence and one article listed reasons for non-adherence. Six studies suggested possible interventions to improve adherence. Schneeweiss et al showed that insurance type influences statin adherence among new statin users. Patients with full coverage insurance were more adherent to their statin

medication, than those with copayment insurance or coinsurance (4). Benner et al Studied retrospectively 19422 statin users in regard to frequent follow up by physicians and lipid testing. The study showed that early and frequent follow up by physicians and lipid testing were associated with higher rates of adherence to therapy. Patients who had follow up and lipid testing were 45% more likely to be adherent (5). One Turkish study showed reasons for non-adherence among coronary artery disease patients. Among these reasons was: 60 % due to physician discontinuation, 14% due to cholesterol levels lowered or reached goal, 9% due to patient liking to take the pill, 8% due to negative information received from TV programs and social media, 5% due to fear of liver toxicity and 4% due to difficulty obtaining the drug from the pharmacy (6). SRBM Eussen et al. assessed the adherence of 439 new statin user by discontinuation rate and medication possession ratio after 6 and 12 months of therapy initiation. The intervention group, n=439, was given pharmacist counseling sessions five times a year about the importance of medication adherence, lipid levels management, and association between adherence and lipid levels. The counseling sessions were done at first prescription, 15 days, 3 months, 6 months, and 12 months refill. The control group, n=460, received the usual care without extensive pharmacist counseling session. The result showed the 6 months discontinuation rate significantly lower in the intervention group, however no difference after 12 months between the two groups. No significant difference between the two groups in regard to the medication possession ratio was found (7). Yilmaz et al. studied 203 patients on statin therapy as a secondary prevention. The intervention group consisted of 102 patients who received information on statins importance, pharmacology, side effect, statin role in mortality and morbidity benefits. Participants questions were answered, and information were given in a free conversational way, and no structured information method was followed. The control group n=101 did not receive any further information upon their therapy. After 15 months patients were evaluated for adherence to statin therapy, appearance of any side effect, fasting lipid profile including triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol, which was calculated via Friedwald formula. The study showed 64.7% of informed group reached the LDL target level whereas, 43% of those in non-informed group reached the target. 62.7% of patients in the informed group were adherent to

therapy, whereas, only 46% of patients in non-informed group were adherent (8). One study assessed physician-patient cardiovascular risk dialogue to improve statin adherence. The intervention group received a patient – physician education program on cardiovascular risk and importance of statin adherence. By assessing the statin fill prescriptions, the study showed that patients exposed to education programs were 10% more likely to fill prescriptions for at least 120 days (9). Reddy et al. studied 126 patient with coronary artery disease and poor adherence. Patients were randomized to one of three groups for three months. First group was sent daily alarm and weekly feedback report. The second group was sent daily alarm and weekly feedback report to their partner, family member or a friend. The control group had no alarm or feedback. The study showed that individual feedback group had 89 % adherence level, partner feedback group has 86 % adherence level, and control group had 67 % adherence level (10). Two trials studied patients with diabetes on statin with poor adherence. Over three months, adherence was assessed by wireless pill bottle measured by percentage of days with a bottle opening. In the PROMOTE trial patients were randomized to one of three groups. The first group received weekly emails comparing the participants statin adherence with others in the study along with a message of encouragement. The second group received an email summary of their individual adherence report. The third was a control group. In the SUPPORT trial, participants were randomized to one of four groups. In the first group each participant's adherence was reported to another person daily. In the second group weekly. In the third, missed doses were reported to another person. The fourth group was control. The result of the study showed there was no significant difference between the three promote groups. For the support study, no significant deference was found between the groups as well (11). Adherence to statins is important. One study showed the impact of adherence to statin on cardiovascular (CV) morbidity in the form of the incidence of CV events in 97575 new statin users, aged 45 to 75 with no CV disease at baseline from 2001 to 2004. During the three years of follow-up, 53% of the patients had good adherence, 26% had intermediate adherence, while 21% had poor adherence. A 25% relative risk reduction was observed in the CV events in patient with good adherence compared to patient with poor adherence. In addition there was a lower rate of acute coronary

syndrome and acute cerebrovascular disease events in patient with good adherence rate (12). Another study assessed the LDL-cholesterol level in 1066 patients with history of coronary heart disease who started therapy in 2011. 42.3% of patient with high adherence did not reach the goal of $\geq 30\%$ reduction in LDL-cholesterol level. While 54.7% and 79.7% of patients with intermediate and low adherence failed to reach this goal (13).

CONCLUSION:

Many factors may affect the adherence to statin in a positive or negative way. Full insurance coverage, frequent follow up and lipid testing showed a positive impact on adherence. While missing doctor visits, fear of side effects, not liking to use pills, information received via social media and difficulty obtaining medication have a negative impact on adherence. By knowing this, better counseling and planning upon starting therapy is advised. Frequent counseling sessions by pharmacist or physician can improve adherence to statins. Comprehensive information giving to statins users may increase their adherence and the success of reaching the target LDL levels. In addition, educational pamphlet, adherence report or reminders mailed to the patients during therapy period may also increase adherence rate.

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