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The Efficacy and Safety of Statins in the Primary Prevention of Cardiovascular Disease

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THE EFFICACY AND SAFETY OF STATINS IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

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Abstract

Atherosclerotic plaques can form in the blood vessels from particles of cholesterol. These plaques are a major cause of cardiovascular disease and have the ability to result in fatal cardiovascular events. In researching this topic, PubMed, the Cochrane Library, DynaMed, and ClinicalKey were all utilized in finding articles published from 2002 to 2018. There are several organizations with conflicting guidelines recommending the use of statin medications in the primary prevention of cardiovascular disease. The research evaluated discovers data is inconclusive on the benefit of statin medications in this primary prevention as well as the safety of long-term statin use. Some experts have suggested statins are over-prescribed as it is one of the most commonly prescribed medications in the United States. Statin medications continue to be beneficial in the primary prevention of some select patients, but caution should be applied by providers when prescribing this medication to their patients when referring to conflicting population based guidelines. Providers should identify key risk factors and have conversations with their patients on the risks and benefits of statin medications when they are being utilized for the primary prevention of cardiovascular disease.

Keywords: statin, HMG-CoA reductase inhibitor, atorvastatin, rosuvastatin, fluvastatin, pravastatin, lovastatin, primary prevention, cardiovascular disease, CVD, coronary artery disease, adverse effects

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I. Introduction

Overview of Topic

Atherosclerotic plaques can form in the blood vessels from particles of cholesterol. These plaques are a major cause of cardiovascular disease (CVD) and have the ability to result in fatal cardiovascular events. The cause of this plaque formation is not fully known, but result in narrowing and possible occlusion of blood vessels leading to decreased blood supply to the tissues. This lack of blood flow results in damage to the existing tissues. If a patient has previously had a cardiovascular event or has been diagnosed with CVD, medications to lower cholesterol are used as secondary prevention to prevent further cardiovascular events or worsening of the CVD. If a patient does not have CVD, statins are used in those determined to be at a high risk of developing CVD or having a cardiovascular event (Baron, 2017). The data is inconclusive and differ among many studies whether the use of statins is beneficial in primary prevention when evaluating the rate of cardiovascular events, CVD mortality and all-cause mortality.

Medications that fall into this class of pharmacological agents are commonly referred to as statins and include lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin. Statins are also known as 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors which gives a brief description of their mechanism of action. HMG-CoA reductase is an enzyme involved in the first step in the formation of cholesterol in the liver. By inhibiting HMG-CoA, the synthesis of cholesterol is reduced, thereby reducing the levels of cholesterol found in the blood (Malloy & Kane, 2015). With less cholesterol in the blood, atherosclerotic plaques are not as easily formed. Although, as discussed earlier, the cause of the

formation of plaque is not fully known and increased levels of cholesterol in the blood can increase the likelihood of plaques forming.

Several different organizations have recommendation guidelines to choose patients who may benefit from a statin prescription. The American College of Cardiology (ACC) and American Heart Association (AHA) teamed up to develop a risk assessment calculator. Based on the percentage of risk of developing cardiovascular disease, the calculator then recommends if statins are appropriate for patients. The United States Preventative Services Task Force also uses this risk assessment calculator to divide patients into groups to recommend or not recommend statin therapies. With these differing recommendation statements, some patients fall into a statin therapy benefit group with one organization, but not the other (Pagidaipati, 2017). These population-based recommendations have been criticized as it may seem almost all patients can fall into one of the treatment groups. The use of statins in the prevention of cardiovascular events is difficult to quantify as we still do not know the exact cause of plaque formation or migration of plaques resulting in cardiovascular events. There is also lack of information on whether statin medications have deleterious long-term effects as the widespread use of statins has been somewhat recent in terms of medical research as statins were first approved for use in 1987 (Baron, 2017).

Statement of the Problem

Statin medications have become a mainstay in the primary prevention of CVD. Controversy exists on whether cardiovascular events are truly being prevented by the use of statins or if these medications are being over-prescribed.

Research Question

In patients without existing cardiovascular disease, does taking a statin medication (rather than not taking a statin medication) prevent cardiovascular events?

In patients taking statins, does the benefit of taking statins outweigh the risk of long-term statin use in the primary prevention of cardiovascular disease?

Steps of How Review Was Conducted

In researching this topic, PubMed, the Cochrane Library, DynaMed, and ClinicalKey were all utilized. Keywords searched included: statin, HMG-CoA reductase inhibitor, atorvastatin, rosuvastatin, fluvastatin, pravastatin, lovastatin, primary prevention, cardiovascular disease, CVD, coronary artery disease, adverse effects, pharmacology, and intensity. Several of these keywords were combined applying the Boolean operator "AND" to limit the search. All studies included were published in a peer-reviewed source within the last 15 years.

Organization of Chapters

The Introductory section provided a description of the problem and provided pharmacological information on statin medications. The Review of Literature section provides information about current recommendations for statin use as well as information from several peer-reviewed studies which relate to the use of statin medications and the safety of long-term statin use. The Discussion section will provide a conversation of these articles and how they relate to the primary prevention of cardiovascular disease. Lastly, the Applicability to Clinical Practice section will focus on providing practitioners with information on choosing which patients are ideal candidates for statin medications and which patients may not see benefit from their use.

II. Review of Literature

Background Information

The efficacy of statins and their effect on cholesterol is determined by evaluating lipids. Lipids in the plasma are found in complexes called lipoproteins. These can be further divided into low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides. Lipid levels are evaluated in patients after a ten hour fast to avoid alterations in measurements caused by food consumption. LDL cholesterol levels, the primary target of statin medications, should be below 100 mg/dL, whereas levels above 190 mg/dL are considered very high. HDL cholesterol levels are inverse to LDL cholesterol, in which higher levels are optimal. These levels are best when measured above 60 mg/dL. Total cholesterol levels are calculated based on an equation adding LDL levels, HDL levels and one-fifth of the triglyceride levels. Total cholesterol levels below 200 mg/dL are desired. High levels of lipids in the blood is commonly referred to as dyslipidemia or hyperlipidemia. Atherosclerosis is a substantial concern related to long-term dyslipidemia (Malloy & Kane, 2015).

The pharmacodynamics of statins is also important when evaluating this class of medications, especially when discussing safety. Once statins have been administered, there is significant first-pass hepatic uptake. Hepatic synthesis of cholesterol is most active during the night, so statins with a low half-life should be administered in the evening. Once entering the liver, more than 70% of the medication is excreted by the liver and into the feces. Some adverse effects, although rare, include headache, nausea, constipation, myopathy, and elevations in liver function tests. Patients should avoid taking statin medications if they are pregnant or breastfeeding, if they have unexplained elevated liver function tests, or if they have active liver disease. Providers should also take caution in patients with long-term alcohol use.

Recommendations for statin prescribing include obtaining a creatinine level and liver function tests at baseline and then as clinically indicated (Gurgle & Blumenthal, 2017).

Statins can be classified by their intensity, or to what degree of LDL cholesterol lowering is expected. High-intensity statins include atorvastatin (40 or 80 mg) and rosuvastatin (20 or 40 mg). These lower LDL cholesterol concentrations by an estimated 50% or more. Moderate-intensity statins include atorvastatin (10 or 20 mg), fluvastatin (40 mg twice daily), lovastatin (40 mg), pravastatin (40 or 80 mg), rosuvastatin (5 or 10 mg) and simvastatin (20 or 40 mg). These affect LDL cholesterol by lowering concentrations by about 30 to 50%. Low-intensity statins include lovastatin (20 mg) and pravastatin (10 or 20 mg) and can lower LDL cholesterol concentrations by less than 30% (Gurgle & Blumenthal, 2017).

Current Recommendations of Statin Use

Recommendations for use of statins vary among different professional agencies. First, it is essential to determine which patients may be at an increased risk for developing CVD. Many divide their recommendations by stratifying patients based on their 10-year atherosclerotic cardiovascular disease (ASCVD) risk. The American Heart Association (AHA) and American College of Cardiology (ACC) have developed a risk score calculator to help providers determine which patients may be at an increased risk of developing CVD. This calculator uses the patient's age, race, sex, cholesterol levels, history of diabetes, use of hypertension treatment, smoking status to determine a patient's risk score. DeFilippis, Young, and Blaha (2015) evaluated the most commonly used AHA/ACC ASCVD risk score with four other risk scores calculators to compare their efficacy. In the 4,227 patients with a mean age of 61.5 years were evaluated after an approximate ten-year follow up. The researchers discovered four out of the five risk stratification tools overestimated risk in men by 37% to 154%. Risk was overestimated for

women in three of the five tools by 46% to 67%. For example, there were 387 people who were predicted to have a 10% probability of having an ASCVD event according to the AHA/ACC ASCVD risk calculator during the ten-year study with 218 people having an event. ASCVD events were better predicted in women than in men. This brings up a possibility of overestimating a patient's risk when using these calculators, but this is certainly better than underestimating. This study is a ten-year snapshot of a patient's life, whereas it will be interesting to see trials with longer evaluation periods.

After determining a patient's increased risk, several organizations have recommendations on who should be taking statin medications. The United States Preventative Services Task Force (USPSTF) recommend the use of statins in the primary prevention of CVD with conditions deemed to increase the patient's risk including diabetes, dyslipidemia, early cerebrovascular disease, hypertension, mild to moderate aortic stenosis, microalbuminuria, and elevated C-reactive protein (CRP) levels. They state all adults aged 40 to 75 years without a prior history of CVD with one or more CVD risk factors and a calculated 10-year ACC/AHA ASCVD risk of 10% or greater should be taking a low- to moderate-intensity statin for primary prevention purposes. They classify this recommendation as a Grade B Recommendation which suggests there is a high certainty of moderate benefit or there is moderate certainty of moderate to substantial benefit. If a patient has a lower ACC/AHA ASCVD risk below 10% but above 7.5%, statin use for primary prevention provides a smaller benefit. This is a Grade C Recommendation which allows the health professional to use their judgment on individual circumstances if recommending use would be beneficial to the patient (Chou, Dana, Blazina, Daeges, & Jeanne, 2016).

Other recommendations for statin use have been proposed by the ACC and AHA. They highlight four groups that would benefit from statins including those with ASCVD, those who are greater than 21 years of age with LDL cholesterol levels greater than 190 mg/dL, those with diabetes mellitus who are between 40 and 75 years of age with LDL cholesterol levels between 70 to 189 mg/dL, and those without ASCVD or diabetes or LDL cholesterol levels greater than 190 mg/dL and an estimated 10-year ASCVD risk of greater than 7.5%. Prior to this report, it was suggested patients be treated to a specific goal LDL cholesterol target level. With this report, the ACC/AHA Expert Panel recommends using the maximum tolerated statin intensity. For primary prevention, they recommend at least a moderate-intensity statin in all cases falling into the statin benefit groups (Stone et al., 2014).

When evaluating the differences among ACC/AHA and USPSTF recommendation statements, Pagidaipati (2017) looked at a sample of 3,416 subjects aged 40 to 75 years without prior CVD. In this population, 21.5% of the subjects were taking stating medications and an additional 15.8% of the subjects would be eligible based on the USPSTF guidelines compared to an additional 24.3% when looking at the ACC/AHA guidelines. Much of the discrepancy is due to the ACC/AHA guidelines recommending statin therapy in those with diabetes and the USPSTF guidelines do not. Others who were covered under the ACC/AHA guidelines but not the USPSTF guidelines included younger male smokers, younger males with dyslipidemia and younger women with obesity.

The European Society of Cardiology (ESC) has yet another set of guidelines to determine if patients are at high risk of fatal CVD and should be taking statin medications in an effort of prevention. The ESC uses a risk stratification tool called the Systematic Coronary Risk Evaluation (SCORE) to determine the 10-year risk of fatal CVD rather than the use of the

ACC/AHA ASCVD risk tool commonly used in the United States. It bases its recommendation on the systolic blood pressure, age, gender, smoking status and total cholesterol as well as which country the patient lives in. Certain countries in Europe, including Denmark, France, Germany, Italy, Norway, Spain and others, are at a lower risk compared to countries such as Armenia, Bulgaria, Russia, and Ukraine. These differences in country of origin may be associated with diet, genetics, or other factors. Statin treatment is recommended in patients if the 10-year risk of fatal CVD is 5-10% and LDL-C is above 100 mg/dL or if the 10-year risk is greater than 10% and the LDL-C is above 70 mg/dL. Pavlovic et al. (2016) compared the ACC/AHA recommendation guidelines to that of the ESC. The study included 7,279 individuals without CVD and ages between 45 and 75 years. The ACC/AHA guidelines using the ASCVD risk calculator would recommend 58.9% of the patients be on a statin treatment, where the ESC guidelines would recommend 33.0% of the patients be treated with statins. The researchers discussed that many of those qualifying for the ACC/AHA guidelines but not the ESC guidelines were younger women with lower lipid profiles.

Statin and Placebo Comparisons in Primary Prevention of Cardiovascular Disease

It is well-known that statin medications decrease levels of LDL cholesterol. Several studies have evaluated the efficacy of statins in preventing cardiovascular effects in comparison to a placebo. Many of these trials have included patients with pre-existing conditions which qualify them for statin therapy in the primary prevention of CVD.

Hypertension.

In patients with pre-existing conditions putting them at an increased risk, statins may be of benefit. An elevated blood pressure puts a strain on the heart and can damage blood vessels possibly putting a patient at an increased risk of serious health problems including myocardial

infarction or a cerebrovascular accident. The researchers in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) (2002) compared the use of pravastatin 40 mg, a moderate-intensity statin, to a usual care control group in the treatment of lipid-lowering and the effect on all-cause mortality. The randomized, nonblinded trial included subjects with hypertension with fasting LDL cholesterol levels of 120 to 189 mg/dL. The mean age of the population at the start of the study was 66 years, with 49% of the subjects being female and 41% of subjects being white. A total of 10,355 participants were included in the study and their treatment was evaluated for up to eight years. The researchers concluded there was no significant difference in all-cause mortality when comparing pravastatin treatment to usual care ($p = 0.88$). The rate of coronary heart disease was slightly lower in the pravastatin group ($p = 0.16$).

Diabetes mellitus.

Diabetes mellitus is another comorbidity that can increase a patient's risk of developing CVD. Heljić, Velija, and Kulić (2009) evaluated the use of statins in the primary prevention of coronary heart disease in patients with pre-existing type 2 diabetes mellitus. The trial evaluated the levels of cholesterol as well as CRP in 95 subjects. CRP is an inflammatory marker which has been linked to atherosclerotic plaque formation in blood vessels. They excluded patients with serious comorbidities such as heart, liver, or kidney problems, hemoglobin A1c (HgbA1c) levels greater than ten percent, a body mass index greater than 35 kg/m^2, and blood pressure greater than 140/90 mmHg. They split the subjects into two groups, one taking simvastatin 40 mg, a moderate intensity statin, and one taking a placebo. The mean age of the population was 61 years with 58% of the subjects being female. The researchers did not report the race of the subjects. After the one-year trial, the group taking simvastatin had significantly lower CRP levels than the

placebo group ($p < 0.01$). Coronary events were rarer in the simvastatin group ($n = 3$) than in the placebo group ($n = 7$). The researchers concluded that statin therapy reduced the risk of coronary heart disease by decreasing CRP levels. With only 95 subjects, it is difficult to compare and correlate the findings with trials exceeding 10,000 subjects. This study is beneficial in that it discusses the use of CRP to evaluate the efficacy of prevention of CVD.

Another study performed by Knopp, d'Emden, Smilde, and Pocock (2006) evaluated the effects of atorvastatin 10 mg, a moderate-intensity statin, to a placebo in 2,410 subjects with type 2 diabetes in a double-blind, placebo-controlled four-year study. The mean age of the population was 60 years with 38% of the subjects being female and 84% of subjects being white. They evaluated the two groups by assessing a primary cardiovascular end point by defining those who had a cardiovascular death, a nonfatal myocardial infarction, a nonfatal stroke, recanalization, coronary artery bypass surgery, a resuscitated cardiac arrest and worsening or unstable angina requiring hospitalization. The atorvastatin group noted a mean 29% LDL cholesterol reduction ($p < 0.0001$). In the group of patients who had not had a previous cardiac event, 10.4% of those taking atorvastatin and 10.8% of those treated by the placebo experienced a primary end point. The relative risk reduction was found to be 19% ($p = 0.41$). They concluded their results to be not statistically significant and could not determine a confirmed benefit of statin therapy in the primary prevention of CVD in patients with type 2 diabetes.

In addition to diabetes, other comorbidities may put patients at a further increased risk of developing CVD. Colhoun et al. (2004) identified patients with type 2 diabetes who had at least one other comorbidity including hypertension, retinopathy, microalbuminuria, or currently smoking. Patients were excluded from the study if they had any history of myocardial infarction, angina, coronary vascular disease, cerebrovascular accident, or severe peripheral vascular

disease. A total of 2,838 patients were involved in the four-year trial. The mean age of the population was 62 years, with 32% of the subjects being female and 95% of subjects being white. Patients were divided into two groups; one taking atorvastatin 10 mg, a moderate intensity statin, and one taking a placebo. They observed a reduction of 36% in acute coronary events, 31% decrease in coronary revascularization events, and 48% decrease in stroke in those taking the atorvastatin. The researchers also found in the atorvastatin group that a 37% reduction in major cardiovascular events ($p = 0.001$) and a 48% reduction in stroke occurred. Of note, the trial was ended early due to what the researchers felt was a significant reduction found on all-cause mortality in the atorvastatin group. The researchers also describe significant effects on all-cause mortality which promotes the use of statin therapy in the primary prevention of CVD in patients who may have multiple risk factors.

Other risk factors.

Yusuf et al. (2016) evaluated effects of rosuvastatin 10 mg, a moderate-intensity statin, compared to a placebo on the primary prevention of cardiovascular events on patients with intermediate risk factors in a double-blinded, randomized trial in 228 centers in 21 countries. Participants in the trial were greater than 55 years of age if male or greater than 65 years of age if female and were required to have one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of a low level of HDL cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary artery disease, or mild renal dysfunction. The mean age of the population was 66 years, with 46% of the subjects being female and 20% of subjects being white. After the seven-year study including 12,705 persons, the LDL cholesterol level was 34.7 mg/dL lower in the rosuvastatin group than in the placebo group ($p < 0.001$). An outcome or event was determined to be a cardiovascular death, a nonfatal stroke or a nonfatal

myocardial infarction. An event occurred in 3.7% of the participants in the rosuvastatin group and 4.8% of the participants in the placebo group (p=0.002). This resulted in a number needed to treat with rosuvastatin to prevent one event to be 91. This study highlights a more multi-cultural participant population and noted no differences in findings across several backgrounds. With a moderate-intensity fixed-dose statin utilized in this study, it may indicate even a simple approach to treatment without monitoring may be effective.

In evaluating the differences of statins in whites and nonwhites, Albert et al. (2011) evaluated an already completed a randomized, double-blind, placebo-controlled trial of 17,802 subjects. The researchers compared rosuvastatin 20 mg, a high-intensity statin, to a placebo on their effects of LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) levels. Subjects were all healthy at the start of the trial without prior known CVD, diabetes, or hyperlipidemia. The mean age of the population was 66 years, with 39% of the subjects being female and 71% of subjects being white. Results included a 45% reduction in cardiovascular events in whites and a 37% reduction in nonwhites. This study included 5,117 nonwhite subjects which is much higher than many of the other studies. This may suggest statins are not as effective in the nonwhite population.

Age should also be considered when evaluating if a patient should be taking a statin medication. It is well known that medications exert their effects differently in older individuals and with many of the side effects of statins including muscle problems and brain fogginess, it may be concerning to have these effects increased in the elderly population as it could have the potential to result in negative effects on function and may increase the risk for falls or other catastrophic events. Han et al. (2017) evaluated the patients in the ALLHAT trial who were 65 years of age and older without ASCVD at the start of the trial. In the 2,867 patients evaluated,

more participants died in the pravastatin group when compared to the usual care group in ages 65 to 74 years (p=0.55) as well as those older than 75 years (p = 0.07). They concluded that statin use for primary prevention did not have a benefit on all-cause mortality or coronary heart disease when comparing to usual care in patients older than 65 years of age. Although a nonsignificant correlation, they did note an increase in all-cause mortality with the use of pravastatin in those greater than 75 years. After one year, 8.3% of the usual care group were taking a statin and this increased to 29% in the sixth year.

As noted with the comparison of the ESC guidelines in other countries to the ACC/AHA and USPSTF guidelines, it is known that statins are used much more frequently in the United States than in other countries. It is not known if this is due to the American diet and lifestyle or if other countries are not utilizing the medication as frequently. Nakamura et al. (2006) performed a study to evaluate if research done on western populations can be applied to patient in Japan, where the rate of CVD is much lower. The randomized, blinded study included 7,832 patients with preexisting hyperlipidemia were split into a diet group and a diet plus pravastatin group. The mean age of the population was 58 years with 69% of the subjects being female. Pravastatin 10 mg, a low-intensity statin, was administered initially to the treatment group and adjusted up to 40 mg if deemed to be appropriate by the treating physician. Coronary heart disease and cerebral infarction occurred at a significantly lower rate in the pravastatin group (p = 0.005). The rate of all cardiovascular events was also significantly lower in the pravastatin group (p = 0.01). The researchers found the number needed to treat to prevent one coronary heart disease event was 119 in the Japanese subjects. Although the trial used a low-intensity statin, the researchers deemed there was a significant benefit in the use of statin therapy in patients with hyperlipidemia.

Vascular effects of statin medications.

The thickness of the vessels, specifically the carotid intima-media thickness (IMT), and the left ventricular mass has also been proposed to evaluate the benefits of statins. Increased carotid IMT has been shown to be predictive of the development of coronary artery disease, stroke, and coronary atherosclerosis. Anderssen, Hjelstuen, Hjermann, Bjerkan, and Holme (2005) performed a study in 568 drug-treated hypertensive subjects over the course of four years. The mean age of the population was 57 years with all subjects being male. There were four groups evaluated in the study. One group was given fluvastatin 40 mg, a low-intensity statin, another group was given a placebo, a third group was given fluvastatin and instructed on lifestyle interventions and a final group was given a placebo and given lifestyle interventions. The lifestyle interventions included physical activity as well as dietary intervention programs. When evaluating the effect of fluvastatin alone to the placebo, there was significantly reduced progression in common carotid artery IMT ($p = 0.0297$). Fluvastatin also significantly reduced the progression of common carotid artery IMT when comparing the groups of fluvastatin with lifestyle intervention and those with only lifestyle interventions ($p = 0.0214$). The left ventricular mass in placebo-treated patients increased by 30.4 grams over the course of the trial. This increase in mass did not occur with subjects being treated with fluvastatin which was found to be statistically significant ($p = 0.0144$).

Another study evaluating the carotid intima-media thickness was performed on patients with type 2 diabetes mellitus. Beishuizen (2004) evaluated 250 diabetic patients in their trial. The mean age of the population was 59 years, with 53% of the subjects being female and 68% of subjects being white. The subjects were divided evenly into a statin group and placebo group. The statin group started on cerivastatin 0.4 mg which was switched to simvastatin 20 mg, a

moderate-intensity statin, in the middle of the study when cerivastatin was withdrawn from the market. LDL cholesterol increased by 8% in the placebo group and was reduced by 25% in the statin group ($p < 0.001$). The carotid IMT in the placebo group was 0.780 mm at baseline and 0.774 mm at two years ($p = 0.50$), while the carotid IMT in the statin group was 0.763 mm at baseline and 0.765 mm at two years ($p = 0.78$). There was no statistically significant change in the IMT when comparing the two groups ($p = 0.48$). They concluded atherosclerosis progression, when evaluating common carotid IMT, was mild in both groups, which they stated was unexpected. They did describe a significant lowering of LDL cholesterol with the use of the moderate-intensity statin, which would be expected.

Safety of Long-Term Statin Use

When utilizing a medication in the primary prevention of disease, it is important to evaluate the safety of the medication as the risk versus benefit in patients should always be considered. When looking at adverse effects of statin medications, Collins et al. (2016) concluded in 10,000 patients, there may be 5 cases of myopathy, 50 to 100 new cases of diabetes mellitus, and 5 to 10 hemorrhagic strokes. These adverse effects were deemed to be minimal compared to the possible risks of not taking a statin, such as having a fatal cardiovascular event.

In patients taking statins, Crandall et al. (2017) discuss the incidence of diabetes in patients who are not diabetic and start a statin medication. They performed a trial with 3,234 participants who were older than 25 years of age, had a BMI greater than 24 kg/m^2 and had fasting plasma glucose levels between 95 and 125 mg/dL as well as an impaired glucose tolerance test. Participants were assigned to one of three groups including intensive lifestyle interventions, metformin, or a placebo. After 10 years, 33 to 37% of subjects had started a statin medication prior to their diabetes diagnosis, most commonly simvastatin or atorvastatin. The

researchers concluded that statin use may be a risk factor for developing diabetes in patients who are at high risk. They suggested if statins are started on a high-risk patient, that the patient is monitored closely. This study discusses the use of statin therapy in patients who are at a high risk of developing diabetes and states statins may increase that risk.

III. Discussion

Cardiovascular disease (CVD) is a leading cause of death in the United States in both men and women. The medical community is continuously looking for methods of preventing CVD and keeping patients healthy. One constant in the research has been the development of atherosclerotic plaques when there are elevated levels of cholesterol in the blood. The exact cause of the development of the plaques is unknown, but lower levels of cholesterol often lead to lower atherosclerotic plaque formation, which in turn reduces the risk for having a cardiovascular event. Statin medications have long been known to decrease cholesterol levels by decreasing the rate-limiting enzyme, HMG-CoA reductase, in the formation of cholesterol. With this information, statin have been prescribed to prevent cardiovascular events, especially in those with a history of CVD, also known as secondary prevention. In primary prevention, or attempting to prevent CVD before it occurs, it has been difficult to determine if the widespread population-based use of statins recommended by several health organizations is resulting in decreased risk of developing cardiovascular disease.

The American College of Cardiology (ACC) and the American Heart Association (AHA) developed a risk assessment calculator to determine a person's risk of developing cardiovascular disease. This risk is based on age, race, blood pressure, levels of low-density lipoprotein, and other comorbidities such as diabetes mellitus and hypertension. DeFilippis et al. (2015) concluded this calculator, along with other CVD risk calculators, may be overestimating risk by 25 to 152 percent. The United States Preventative Services Task Force (USPSTF) uses the ACC/AHA risk assessment tool to predict whether statin medications will be beneficial to a patient population. A risk of 10% or higher deems a patient should be taking a low- to moderate-intensity statin (Chou et al., 2016). The ACC/AHA also recommends at least a moderate-

intensity statin in patients who are greater than 21 years of age with LDL cholesterol levels greater than 190 mg/dL, those with diabetes mellitus who are between 40 and 75 years of age with LDL cholesterol levels between 70 to 189 mg/dL, and those without ASCVD or diabetes or LDL cholesterol levels greater than 190 mg/dL and an estimated 10-year ASCVD risk of greater than 7.5% (Stone et al., 2014). The use of these population-based tools to determine the likelihood of a medication helping a certain patient has been under scrutiny in recent years. Each of these recommendation statements differs and some patients may be a candidate for statins with one tool, but not the other. Pagidaipati (2017) evaluated the differences in these two recommendation statements and concluded in those not taking statins, an additional 15.8% of the subjects would be eligible based on the USPSTF guidelines compared to an additional 24.3% when looking at the ACC/AHA guidelines. Much of the discrepancy is due to the ACC/AHA guidelines recommending statin therapy in those with diabetes and the USPSTF guidelines do not. The inconsistency of these recommendation statements can make it confusing for providers who may be prescribing these medications.

A study performed by Heljić et al. (2009) evaluated patients with diabetes mellitus and compared the effects of a moderate-intensity statin and a placebo on CRP levels in 95 patients. After the one-year trial, the group taking simvastatin had significantly lower CRP levels than the placebo group ($p < 0.01$). Although this study had only 95 patients, it does bring up the possibility of evaluating CRP levels as a means to predict potential cardiovascular events. This study also was only performed over the course of one year, which may not be enough to determine if there is an effect on prevention of cardiovascular events. In contrast, another study performed on diabetic patients, assessed the primary cardiovascular end point in 2,410 subjects. In the four-year study, 10.4% of those taking the moderate-intensity statin and 10.8% of those

treated by the placebo experienced a primary end point. The relative risk reduction was found to be 19% ($p = 0.41$). They concluded their results to be not statistically significant and could not determine a confirmed benefit of statin therapy in the primary prevention of CVD in patients with diabetes (Knopp et al., 2006). With diabetes being the inconsistency between the USPSTF guidelines and the ACC/AHA guidelines, this study brings up the possibility of statins not being as beneficial to patients with diabetes and no other comorbidities. When evaluating diabetes patients who do have other comorbidities such as hypertension, retinopathy, microalbuminuria, or currently smoking, Colhoun et al. (2004) evaluated 2,838 patients over a four-year trial while the patients were taking either a moderate intensity statin or a placebo. They observed a reduction of 36% in acute coronary events, 31% decrease in coronary revascularization events, and 48% decrease in stroke in those taking the atorvastatin. The researchers also found in the atorvastatin group that a 37% reduction in major cardiovascular events ($p = 0.001$) and a 48% reduction in stroke occurred. Of note, the trial was ended early due to what the researchers felt was a significant reduction found on all-cause mortality in the statin group. The researchers also describe significant effects on all-cause mortality which promotes the use of statin therapy in the primary prevention of CVD in patients who may have multiple risk factors. It is these multiple risk factors that are not included in the ACC/AHA risk assessment tool that may increase certain patients risk even further, but those without multiple risk factors may have an overestimated risk.

In addition to diabetes, other conditions noted to increase risk have been evaluated by researchers. Yusuf et al. (2016) evaluated effects of a moderate-intensity statin compared to a placebo on the primary prevention of cardiovascular events on patients with intermediate risk factors such as elevated waist-to-hip ratio, history of a low level of HDL cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary artery disease, or mild

renal dysfunction. After the seven-year study including 12,705 persons, an event occurred in 3.7% of the participants in the rosuvastatin group and 4.8% of the participants in the placebo group (p=0.002). This resulted in a number needed to treat with rosuvastatin to prevent one event to be 91. This study was performed in a number of different centers across multiple countries and represents a more multi-cultural participant population and noted no differences in findings across several backgrounds. Albert et al. (2011) found conflicting results when evaluating 17,802 subjects with a number of nonwhite subjects. With 5,117 nonwhite subjects, they noted more nonwhite subjects than many of the other similar studies. Results included a 45% reduction in cardiovascular events in whites and a 37% reduction in nonwhites. This may suggest statins are not as effective in the nonwhite population. Further research is needed in this area.

Other ethnic groups may also see different benefits from the use of statin medications. The Nakamura et al. (2006) study aimed to evaluate if research done on western populations can be applied to patients in Japan, where the rate of CVD is much lower. Coronary heart disease and cerebral infarction occurred at a significantly lower rate in the statin group ($p = 0.005$). The rate of all cardiovascular events was also significantly lower in the statin group ($p = 0.01$). The number needed to treat to prevent one coronary heart disease event was 119 in the Japanese subjects with hyperlipidemia. Although the trial used a low-intensity statin, the researchers deemed there was a significant benefit in the use of statin therapy in patients with hyperlipidemia. These patients did not have other comorbidities such as hypertension or diabetes which would potentially increase their risk of cardiovascular events.

Age should also be considered when evaluating if a patient should be taking a statin medication. It is well known that medications exert their effects differently in older individuals and with many of the side effects of statins including muscle problems and brain fogginess, it

may be concerning to have these effects increased in the elderly population as it could have the potential to result in negative effects on function and may increase the risk for falls or other catastrophic events. Han et al. (2017) evaluated a trial of 2,867 patients over the age of 65 and found that more participants died in the statin group when compared to the usual care group in ages 65 to 74 years (p=0.55) as well as those older than 75 years (p = 0.07). The researchers concluded that statin use for primary prevention did not have a benefit on all-cause mortality or coronary heart disease when comparing to usual care in patients older than 65 years of age. Age is certainly a factor to be considered when starting a patient on a new medication, especially if the goal is the prevention of atherosclerotic cardiovascular disease which may already be present at an older age.

Although it is unknown how atherosclerotic plaques form, some researchers have evaluated the thickness of the vessels, specifically the carotid intima-media thickness (IMT) as a way to predict CVD. Increased carotid IMT has been shown to be predictive of the development of coronary artery disease, stroke, and coronary atherosclerosis. In a four-year study comparing a low-intensity statin to a placebo, there was significantly reduced progression in common carotid artery IMT (p = 0.0297). Anderssen et al. (2005) also found the left ventricular mass in placebo-treated patients increased by 30.4 grams over the course of the trial which did not occur in the 568 drug-treated hypertensive subjects (p = 0.0144). Comparing this trial to one performed on patients with diabetes mellitus, Beishuizen (2004) evaluated 250 diabetic patients and discovered the carotid IMT in the placebo group was 0.780 mm at baseline and 0.774 mm at two years (p = 0.50), while the carotid IMT in the statin group was 0.763 mm at baseline and 0.765 mm at two years (p = 0.78). There was no statistically significant change in the IMT when comparing the two groups (p = 0.48). They concluded atherosclerosis progression, when evaluating common

carotid IMT, was mild in both groups, which they stated was unexpected. They did describe a significant lowering of LDL cholesterol with the use of the moderate-intensity statin, which would be expected. This again brings up the possibility of statin medications not being as helpful in patients with diabetes as discussed earlier with the Knopp et al. (2006) trial.

A concern with many of the trials discussed is that the length is often only a few years. The increase of statin prescribing in recent years is concerning due to the lack of research on the safety of long-term statin use. Providers will need to know the long-term safety of the medication when assessing the risk versus benefit in their patients. When looking at adverse effects of statin medications, Collins et al. (2016) concluded in 10,000 patients, there may be 5 cases of myopathy, 50 to 100 new cases of diabetes mellitus, and 5 to 10 hemorrhagic strokes. These adverse effects were deemed to be minimal compared to the possible risks of not taking a statin, such as having a fatal cardiovascular event. Conversely, Crandall et al. (2017) assessed the incidence of diabetes in patients who are not diabetic and start a statin medication. In 3,234 participants who were older than 25 years of age, had a BMI greater than 24 kg/m^2 and had fasting plasma glucose levels between 95 and 125 mg/dL as well as an impaired glucose tolerance test, 33 to 37% of subjects had started a statin medication prior to their diabetes diagnosis over a ten-year period. The researchers concluded that statin use may be a risk factor for developing diabetes in patients who are at high risk. They suggested if statins are started on a high-risk patient, that the patient is monitored closely.

In conclusion, studies still seem to lack true evidence of a reduction cardiovascular events when starting a statin. It is difficult to assess the efficacy of a medication when evaluating its prevention abilities, so it may be more beneficial for providers to prescribe this medication on a case by case basis rather than the population-based recommendation guidelines set out by the

USPSTF and ACC/AHA. Certain population, such as those with diabetes, may not see as much benefit in starting a statin, especially if there are no other comorbidities in the patient. Patients should continue to be monitored for long-term side effects as the safety of extended administration of these medications is still under investigation as the rate of prescribing is growing exponentially.

IV. Applicability of Clinical Practice

The research assessed in this project identifies some discrepancies among recommendation guidelines on the prescription of statin medications in the primary prevention of cardiovascular disease. It is important for providers to be aware of these recommendation guidelines, but to also assess each patient's individual health status and risk assessment. The risk assessment tools do not take into consideration important factors such as diet and exercise, family history, or other comorbidities which may increase or decrease a patient's risk of cardiovascular disease. The research showed benefit in some populations, including those with multiple risk factors. Other populations, such as those with diabetes, did not have a significant benefit which falls against that of the American College of Cardiology (ACC) and American Heart Association (AHA) recommendation guidelines. Providers can use this information to make decisions together with their patients on whether a statin prescription is appropriate. The prescribing of statin medications has increased exponentially in recent years, making them one of the most commonly prescribed medications in the United States. Their use is relatively new to the pharmaceutical world as they were first introduced in 1987. Long-term use, such as greater than 15 years, of these medications, have yet to be evaluated and is also a consideration providers should take into account when discussing risks with their patients. As patients are diagnosed with conditions such as diabetes at much younger ages, long-term use of statins will become more dominant. Side effects should be frequently discussed and risks should be assessed regularly to determine if removing the medication would be appropriate. Providers must assess each patient's benefits versus risk to determine if a statin prescription may have an effect on the primary prevention of cardiovascular disease. With greatest benefit seen in patients with multiple

risk factors, patients with single risk factors may have the greatest effect in the risk versus benefit discussion when determining statin appropriateness in patient care.

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