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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 extremely beneficial in the secondary prevention of cardiovascular events, but caution should be applied by providers when prescribing this medication to their patients for primary prevention 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.

## Introduction

- Atherosclerotic plaques 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 (Baron, 2017).
- Data is inconclusive and differ among many studies whether the use of statins is beneficial in primary prevention when evaluating the rate of CV events, CVD mortality and all-cause mortality.
- HMG-CoA reductase is an enzyme involved in the first step in the formation of cholesterol in the liver. By inhibiting HMG-CoA (the mechanism of statin medications), 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.
- Conflicting recommendation statements can make it difficult for providers to know which patients fall into a statin therapy benefit group. Some patients may fall into a statin therapy benefit group with one organization, but not another (Pagidaipati, 2017).
- 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?

## Literature Review

- DeFilippis, Young, and Blaha (2015) evaluated the AHA/ACC ASCVD risk score with 4 other risk scores calculators to compare their efficacy. In the 4,227 patients evaluated, the researchers discovered 4 out of the 5 risk stratification tools overestimated risk in men by 37% to 154% and 46% to 67% in 3 out of the 5 tools in women. ASCVD events were better predicted in women than in men.
- Pagidaipati (2017) evaluated 3,416 subjects aged 40 to 75 years without prior CVD. In this population, 21.5% of the subjects were taking statin 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.
- ALLHAT (2002) compared patients with existing HTN with fasting LDL cholesterol levels of 120 to 189 mg/dL. 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 ( $p = 0.88$ ).
- Knopp, d'Emden, Smilde, and Pocock (2006) evaluated 2,410 subjects with T2DM by assessing a primary CV end point by defining those who had a CV death, a nonfatal MI, a nonfatal CVA, recanalization, CABG, a resuscitated cardiac arrest and worsening or unstable angina requiring hospitalization. 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% which was not significant ( $p = 0.41$ ).
- Colhoun et al. (2004) identified 2,838 patients with T2DM who had 1+ comorbidity including HTN, retinopathy, microalbuminuria, or currently smoking. 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 CV events ( $p = 0.001$ ) and a 48% reduction in stroke occurred.
- Yusuf et al. (2016) evaluated 12,705 participants in 228 centers in 21 countries. Who were >55 years of age if male or >65 years of age if female with 1+ of the following CVD risk factors: elevated waist-to-hip ratio, history of a low level of HDL-C, current or recent tobacco use, dysglycemia, FMH of premature CAD, or mild renal dysfunction. After 7 years, a CVD 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.
- Anderssen, Hjelstuen, Hjermann, Bjerkan, and Holme (2005) evaluated 568 drug-treated hypertensive subjects over 4 yrs. 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 ( $p = 0.0214$ ).
- Collins et al. (2016) concluded in 10,000 patients taking statin medications, the adverse effects found may be 5 cases of myopathy, 50 to 100 new cases of diabetes mellitus, and 5 to 10 hemorrhagic strokes.
- Crandall et al. (2017) assessed the incidence of diabetes in patients who are not diabetic upon starting a statin. In 3,234 participants who were older than 25 years of age, had a BMI greater than 24 kg/m<sup>2</sup> 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.

## Recommendation Guidelines

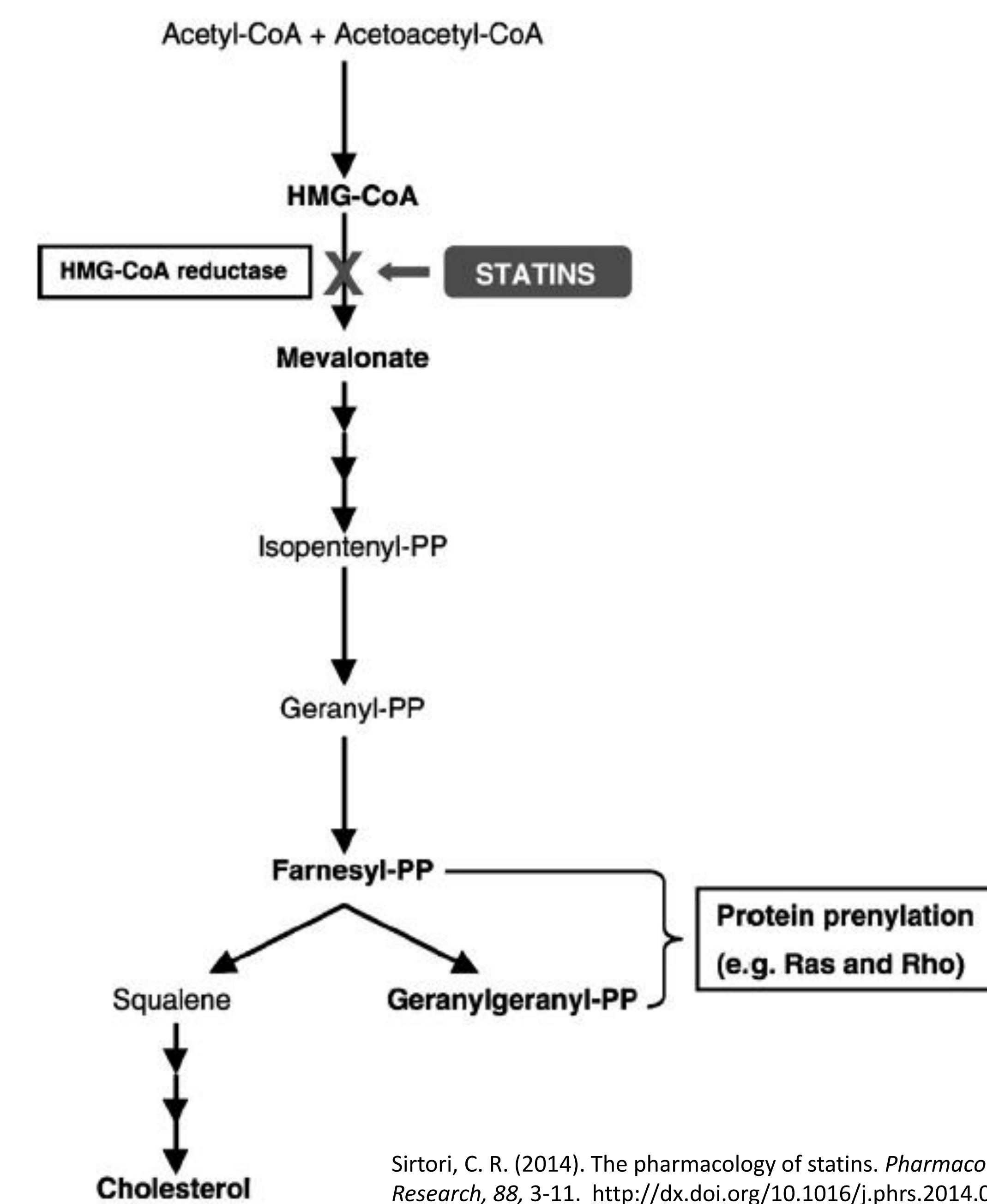
United States Preventative Task Force

- Age 40-75 and ASCVD Risk 10+% (grade B) or ASCVD Risk 7.5+% (grade C)
  - With 1+ Risk Factor (dyslipidemia, diabetes, hypertension, smoker)

American College of Cardiology and American Heart Association

- LDL > 190 mg/dL and Age >21 (grade B)
- Diabetes, Age 40-75 and LDL 70-189 mg/dL (grade A)
- No Diabetes, Age 40-75, LDL 70-189 mg/dL, and ASCVD Risk >7.5% (grade A)
- No Diabetes, Age 40-75, LDL 70-189 mg/dL and ASCVD Risk 5+% (grade B)

## Statin Mechanism of Action



## Discussion

- There are discrepancies among recommendation guidelines on the prescription of statin medications in the primary prevention of CVD.
- 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 CVD.
- The research showed benefit in some populations, especially those with multiple risk factors. Other populations, such as those with diabetes, did not have a significant benefit which falls against that of the ACC/AHA recommendation guidelines.

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## Applicability to Clinical Practice

- Providers can use this information to make decisions together with their patients on whether a statin prescription is appropriate.
- 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 prevalent.
- 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 CVD.
- 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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