

Review Article

Role of statins in primary prevention of cardiovascular disease

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ABSTRACT

Cardiovascular disease continues to remain a global health challenge due to its increasing trend of prevalence. Almost, 6.2 million deaths were caused by cardiovascular diseases among patients of age range 30-70 years in 2019. The burden of cardiovascular diseases can only be reduced by implementation of effective preventive strategies. Primary prevention is of utmost importance since individuals at risk are treated beforehand thus reducing the chance of development of disease. Statins are lipid lowering agents and are used in primary prevention of cardiovascular disease. The purpose of this research is to review the available information about role of statins in primary prevention of cardiovascular disease. Generally, statins are considered as safe and effective medications to treat and reduce the morbidity of cardiovascular diseases. The relative risk of coronary events, cardiovascular disease mortality, non-fatal strokes, and all-cause mortality is decreased with statin therapy. Elderly population or individuals at risk of development of cardiovascular diseases can be efficiently managed by statin therapy. Some studies associate the occurrence of diabetes with the use of statins but most of the studies recommend the role of statins in prevention as benefits outweigh the risks. Literature also supports the role of statins in primary prevention although more clinical studies in future can yield better evidence-based results to support the use of statins especially in primary prevention.

Keywords: Statin, Primary, Prevention, Cardiovascular, Disease

INTRODUCTION

The leading cause of early death and disability in people is cardiovascular disease (CVD), and its prevalence is rising around the globe. Due to their significant impact on the rising cost of healthcare, CVDs also place a significant

socioeconomic burden on the general populace. The pathophysiology and progression of nearly all CVDs are primarily caused by atherosclerosis, which also causes peripheral vascular disease, coronary artery disease, cerebrovascular disease, venous thromboembolism, and myocardial infarction, cardiac arrhythmias, and stroke.

It is well accepted that hyperlipidaemia, hypertension, diabetes, obesity, smoking, and a lack of physical activity are the aetiological risk factors that initiate CVDs. In all epidemiological research, they represent more than 90% of the CVD risks as a group. Despite the high mortality rate of CVDs, the global epidemic of CVDs can be greatly reduced by identifying and carefully avoiding the underlying risk factors.¹ Between the ages of 30 and 70, CVD was responsible for 6.2 million fatalities in 2019. If the world is to fulfil the targets for Sustainable Development Goal 3 and achieve at least a 30% reduction in premature death attributable to noncommunicable diseases, by 2030, it is imperative that we concentrate on adopting current cost-effective interventions and health policies.²

Statins can be used to prevent CVD either directly or indirectly. While secondary prevention involves treating those who already have formed CVD, primary prevention is treating those who do not yet have established CVD but may be at risk of developing it in the future. Statins, also known as 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors, are the first-choice medications for lowering plasma low-density lipoprotein cholesterol and lowering the risk of developing cardiovascular disease. Statin use has significantly increased over the past 30 years, which is consistent with changes in clinical guidelines' recommendations. Although these improvements have served to increase the number of people eligible for treatment, particularly in primary prevention, there is still controversy regarding them.³ European clinical guidelines advise administering atorvastatin at a dose of 20 mg daily or an equal amount of another licensed statin to someone who has a one in ten chance of developing a fatal or non-fatal cardiovascular event in the next 10 years. A cardiovascular risk calculator is used to determine the risk of primary CVD. Age, gender, smoking status, systolic blood pressure, low-density lipoprotein cholesterol level, presence of co-morbid diabetes and hypertension, and some other characteristics are all included in these calculators to determine the risk of CVD. The degree to which a patient adheres to their specified treatment plan after a doctor has prescribed statins directly affects the medicines' efficacy.⁴

In both primary and secondary prevention, statins are typically regarded as safe and effective medications that considerably lower cardiovascular morbidity and death. Statin use is associated with a slight increase in the chance of developing diabetes, albeit this risk seems to be highest in people who already have prediabetes or symptoms of the metabolic syndrome. The risk of adverse events associated with statin primary prevention is greatly outweighed by the decreases in cardiovascular morbidity and death. Patients with minimal risk of 1% estimated annual risk of cardiovascular disease can nevertheless benefit from statin primary prevention in terms of morbidity and mortality.⁵ The purpose of this research is to review the available information about role of statins in primary prevention of CVD.

METHODOLOGY

This study is based on a comprehensive literature search conducted on 28 June 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about role of statins in primary prevention of cardiovascular disease. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

Low-density lipoprotein cholesterol, one of the several forms of cholesterol, is essential for the emergence of atherosclerotic CVD. Catastrophic cardiovascular events are caused by the rupture of atheroma and plaque, which grow and progress as a result of low-density lipoprotein. Statins, which lower cholesterol, work by enhancing low-density lipoprotein clearance from the circulation and reducing low-density lipoprotein synthesis in the liver. Statins are proven to prevent cardiovascular events or mortality in both those with high cholesterol and those who have never experienced cardiovascular disease. The benefits in these populations could be adequately explained by statins' ability to lower cholesterol as well as a number of cholesterol-independent or pleiotropic effects, such as enhanced endothelial function, improved atherosclerotic plaque stability, decreased oxidative stress and inflammation, inhibition of vascular smooth muscle proliferation, and platelet aggregation.⁶

Evidence from literature

Taylor reported in his systematic review findings that with the use of statins, all-cause mortality, fatal and non-fatal CVD events, and the requirement for revascularization through surgery or by angioplasty were all reduced. Treatment lasted at least a year, with a minimum of six months of follow-up. 18 out of 1000 persons taking a statin for five years would avert a major CVD event, which compares favourably to other cardiovascular disease prevention therapies. The risk of significant side effects including cancer was not increased by statin use. In terms of primary prevention, statins are probably cost-effective.⁷ Strandberg stated in his study findings that treatment with statins is only one method for protecting older adults from atherosclerotic CVD. It is advisable to begin treating hypercholesterolemia well before the age of 75 to 80, and there is no need to stop taking statins just because you are becoming older. After 75 years, patients with atherosclerotic CVD should begin treatment, and primary prevention should be used carefully. When palliative care is begun, statin therapy should be stopped, as with all forms of prevention. More knowledge regarding primary

prevention can be gathered from trials and research studies involving people aged 70 and above.⁸

Enas reported that statins have been shown to have a considerable positive impact on CVD outcomes in a number of large double-blind randomized clinical trials, with no appreciable increase in non-CVD mortality. The risk of diabetes and early coronary artery disease is higher in Asian Indians. The available research supports the primary preventive use of statin medication in Asian Indians at younger ages and with lower objectives for low-density lipoprotein cholesterol and non-high density lipoprotein cholesterol than those now advised for Americans and Europeans. The best chance of lowering the ongoing coronary artery disease epidemic among Indians is with early and intensive statin medication.⁹ Reiner stated that the use of statins for the secondary prevention of CVD is well established, but their growing use for the primary prevention of CVD in people without a history of the disease has some drawbacks. First, the evidence suggests that statins significantly lower CVD morbidity in primary prevention, but only mildly lower CVD mortality. Second, prolonged statin treatment may have negative effects, including the emergence of diabetes mellitus. Thirdly, the strategy's cost-effectiveness must be weighed against the danger of overmedicating the general public. Data unambiguously support the use of statins for primary prevention in high-risk people if the method is economical and the advantages outweigh the disadvantages. Primary prevention may or may not be advantageous for those at low or moderate risk. As a result, each patient's statin prescription for primary prevention should be based on clinical judgment, especially for low-risk patients. Statins should also be administered for transient ischemic attack and ischaemic stroke primary prevention in adequately chosen people.¹⁰

Findings of a meta-analysis revealed that statins significantly decreased the chances of nonfatal myocardial infarction (relative risk (RR) 0.75, 95% confidence interval (CI) 0.59-0.94), total (RR 0.74, 95%CI 0.61-0.90), and composite major adverse cardiovascular events (RR 0.82, 95% CI 0.74-0.92). Statin treatment effects on fatal myocardial infarction (RR 0.43, 95% CI 0.09-2.01), stroke (fatal: RR 0.76, 95% CI 0.24-2.45; nonfatal: RR 0.76, 95% CI 0.53-1.11; total: RR 0.85, 95% CI 0.68-1.06), and all-cause mortality were statistically negligible (RR 0.96, 95% CI 0.88-1.04). Myalgia (RR 0.88, 95%CI 0.69-1.13), increased hepatic transaminases (RR 0.98, 95% CI 0.71-1.34), newly diagnosed diabetes (RR 1.07, 95% CI 0.77-1.48), major adverse events (RR 1.00, 95% CI 0.97-1.04), and cessation due to adverse events did not show any significant differences (RR 1.10, 95% CI 0.85-1.42).¹¹ Zhou reported in his study findings in 2022 that at baseline, atorvastatin (37.9%) was the most popular statin type, followed by simvastatin (29.6%), rosuvastatin (25.5%), and other statins (7.0%) predominantly pravastatin. The observed differences in all outcomes in comparisons of particular statins according to type and lipophilicity such as lipophilic vs. hydrophilic statin were negligible and not

statistically significant all p values >0.05. When compared to low-or moderate-potency statin use, the use of high-potency statins including atorvastatin and rosuvastatin was only slightly related with a reduced risk of fatal CVD events (hazard ratio: 0.59; 95% CI: 0.35, 1.00).¹²

Results of a population-based cohort study showed that the statin therapy lowered atherosclerotic CVD risk across the coronary risk spectrum from 16–30% in adherent patients' medical possession ratio 70%. The 5-year number needed to treat was 470 and 204 for the risk groups of 5 and 5-7.4%, respectively, and 75 and 62 for the risk categories of 7.5 and 9.9%. Patients with a high 10-year coronary heart disease risk 10–19.9% should continue to get priority statin medication. The majority of patients with intermediate risk could benefit from statin therapy, but given the greater number needed to treat, the treatment choice should be based on the net benefit, safety, and patient desire.¹³ Results of another population-based cohort study depicted that 5970 (14%) of the 42,767 new statin users were above the age of 70. In the highest to lowest proportion of days covered groups, the incident rates of major adverse cardiovascular events, all-cause mortality, and new-onset diabetes mellitus were 16.9%, 16.7%, 9.4%, and 6.3%, 1.7%, and 9.4%, respectively. The highest adherence group percentage of days covered $\geq 75\%$ had adjusted hazard ratios of major adverse cardiovascular events and death that were significantly lower for the older group: 0.71 (0.57-0.88) and 0.68 (0.54-0.84), respectively. The younger group's corresponding hazard ratios were 0.80 (0.68-0.93) and 0.74, which were less favourable (0.58-1.03). The younger group had a higher risk of developing new-onset diabetes mellitus, but not the older group.¹⁴

Tonelli revealed that in adults aged 40 to 75 years, numerous large randomized clinical trials have demonstrated the efficacy and safety of statin therapy for the primary prevention of atherosclerotic CVD. These studies also support the use of 10-year CVD risk as a screening tool for treatment eligibility. In persons older than 75 years, who may be more likely to benefit due to their inherent CVD risk but also face unclear hazards, there remains uncertainty. Statin therapy has been demonstrated to be cost-effective for the primary prevention of atherosclerotic CVD by several high-quality mathematical simulation models. Despite being safe and effective, statins are rarely used for first-line prevention.¹⁵ Siggelkow expressed that the degree to which a patient adheres to a prescribed course of medicine determines how effective statin therapy will be for them. Greater lipid control has been seen in studies with higher statin adherence rates. Numerous observational studies have discovered a beneficial connection between statin adherence and CVD outcomes in both primary and secondary preventive populations. High levels of adherence result in lower future healthcare expenditures by reducing hospitalizations, in addition to the advantages to health outcomes resulting from the effectiveness of statin therapy. Together, increasing statin adherence improves patient and system outcomes.¹⁶

Yeboyo concluded in his study findings that that rosuvastatin and atorvastatin had the best safety profiles and were the most effective at lowering CVD events. In primary prevention populations, all statins demonstrated statistically significant risk reductions for CVD and all-cause mortality while raising the risk for some adverse effects. Although, the benefit-harm profile varied by statin type.¹⁷ Kazi stated that although low to high doses of statin drugs have been tried in primary prevention trials, most trials have compared a single dose with a placebo rather than analysing dose-escalation techniques, and the majority have tested moderate-dose statins. Trials among people with a history of coronary heart disease that were powered to assess various statin intensities across trial arms provide direct evidence for a decreased risk of CVD events with increased statin intensity. The degree of major vascular event reduction is consistently correlated with the size of low-density lipoprotein lowering, according to meta-analyses of trials involving patients with and without atherosclerotic CVD. Future research should prioritize head-to-head comparisons of different statin dosages for primary prevention.¹⁸ Role of statins in primary prevention of CVD is quite defined in literature and many studies support the use of statins for primary prevention, although more randomized clinical trials and studies in future can be beneficial by providing evidence-based results for the effects of statin therapy on prevention.

CONCLUSION

CVD continues to be significant burden of morbidity and mortality worldwide. Despite significant advancements in the treatment of acute CVD, early CVD symptoms are still frequently fatal or cause permanent impairment. Therefore, the best primary prevention should continue to be a top focus and future clinical trials and studies to determine efficacy of statins in primary prevention can further strengthen the literature and aid in reducing the load of disease.

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