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Statin Therapy for The Primary Prevention of Cardiovascular Disease: Pros

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Abstract

Cardiovascular disease (CVD) is the leading cause of death worldwide. Dyslipidemia is one of the causes of cardiovascular disease with a contributor to plaque formation.Statins are a class of drugs that lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. The purpose of statin therapy is to reduce the risk of cardiovascular and associated morbidity and mortality. Statins have a significant impact on reducing atherosclerosis cardiovascular disease. However, primary prevention of ASCVD using statins is debated although statins have several advantages. This review describes the pros of using statins as primary prevention of cardiovascular disease .A comprehensive electronic search was conducted using PubMed, Google Scholar, and ScienceDirect. The search was limited to English-language publications from 2002 to 2021. Hand-searching of relevant journals and reference lists was also performed. It is found that statins can lower cholesterol levels to prevent the formation of atherosclerosis, which then progresses to cardiovascular disease. Recognizing the presence of coronary artery calcium with imaging strategies can guide the initiation of therapy in young adults. Statins have pleiotropic effects to prevent cardiovascular, cost effective, safe, effective, and well tolerated. On the other hand, statins are still debated in older adults. Statins are a primary preventive consideration to reduce morbidity and mortality due to cardiovascular disease.

Keywords: statin, atherosclerosis, primary prevention, and cardiovascular disease

INTRODUCTION

Cardiovascular Disease (CVD) is the leading cause of morbidity and mortality in the United States and is responsible for one of every three deaths.[1] Cardiovascular disease (CVD) is the leading cause of death worldwide.[2] The etiology of CVD is multifactorial and is affected by well-established risk factors, such as age, sex, family history of early-onset CVD, smoking status, and presence and severity of obesity, dyslipidemia, hypertension, and diabetes.[3]

Cholesterol is a primary contributor to plaque formation and is the main target of statin therapy. Cholesterol is carried in the body in the form of lipid and protein particles (lipoproteins). The purpose of statin therapy is to reduce the risk of cardiovascular and associated morbidity and mortality. Statins are a class of drugs that work by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step in the manufacture of cholesterol. Statins reduce LDL-C, TC, and TG levels; slightly increase HDL-C levels; and are also thought to have anti-inflammatory and other plaque stabilization effects.[4]

METHODS

A comprehensive electronic search was performed using PubMed, Google Scholar, and ScienceDirect. The search was limited to English-language publications from 2002 to 2022. A direct search of relevant journals and reference lists was also conducted. Searches include reviews, original papers, and case reports. The exclusion criteria were articles in languages other than English, articles without full access. Keywords used: Statin, Atherosclerosis, Primary prevention, and Cardiovascular disease. The search results were then sorted by title and abstract, followed by reading the full text and eliminating articles that include the exclusion criteria.

STATIN REDUCE CARDIOVASCULAR DISEASE

Statins are a class of drugs that lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Based on clinical trial evidence of efficacy and safety, statins are widely recommended for primary and secondary prevention of cardiovascular disease.[5] Implementation of findings from randomized clinical trials has been translated to population-level cholesterol lowering interventions that have achieved reduction in ASCVD events globally.[6]

STATINS PHARMACOTHERAPY INITIATION

Modifiable cardiovascular risk factors to have premature ASCVD including tobacco use, hypercholesterolemia, hypertension, and/or type 2 diabetes. The prevalence of dyslipidemia is particularly high in young adults, with <15% of young adults maintaining time-weighted average lipid levels considered normal or optimal (LDL cholesterol <100, HDL cholestrol >60 mg/dL, triglycerides < 150 mg/dL).[7] Statin therapy should be considered for adolescents and young adults aged 10 to 39 years with high LDL cholesterol levels (≥160 mg/dL) and very high levels (190 mg/dL /dL).[8]

Reducing the cumulative exposure to LDL cholesterol is important, the development of atherosclerotic plaques is proportional to the absolute plasma LDL cholesterol value.[9]. The individual's total atherosclerotic plaque load is proportional to biological age times the mean untreated LDL cholesterol.[9] The greater the value of cholesterol will increase the risk of myocardial infarction. Reduction of LDL cholesterol from 125mg/dL to 70mg/dL before the age of 40 years can reduce the risk of myocardial infarction and stop the development of atherosclerotic plaque.[9] Statins pharmacotherapy initiation at the right time during the early stages of atherosclerosis and plaque development is very important to prevent the occurrence of ASCVD.[10]

STATINS HAVE PLEIOTROPIC EFFECTS TO PREVENT CARDIOVASCULAR

Atherothrombosis causes ASCVD clinical events, A Complex Interaction Between Atherosclerotic Plaques and Dysfunction Vascular endothelium, oxidized lipoproteins, inflammation and platelets reactivity.[11] It has been postulated that the cardioprotective benefits of statins are in part related to pleiotropic effects that are independent of

LDL-cholesterol lowering.[12] Statins work both innate and adaptive immune responses by reducing the production of inflammatory cytokine, cell adhesion molecule, reactive oxygen species. Statins also alter the expression of nitric oxide synthase Reduces platelet reactivity, promoting endothelium Stability of atherosclerotic plaques.[13] However, These pleiotropic effects lead to improved clinical outcomes in primary prevention not rigorously quantified.

INITIATION OF STATIN THERAPY WITH ASSESSMENT OF IMAGING STRATEGIES

Atherosclerosis is a chronic disease that starts at a younger age. Initiating statin therapy by looking at the radiological threshold still requires further research.[13] Studies show streaks of fat start as early as age two and are strongly associated with nearly all traditional risk factors, including total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic, diastolic blood pressure, body mass index, and smoking.[13] Imaging strategies including vascular ultrasound and non-contrast computed tomography are important for assessing the presence of atherosclerotic plaques. It is important to make the decision to start statin treatment.[14] Individuals with coronary artery calcium (CAC) require twice the amount of statins to prevent ASCVD than individuals without long-term CAC. [15]

One of the final stages of atherosclerosis can be characterized by calcification. The findings show that 10-34% of adults already have CAC as early as the age of 32.[16] The risk of coronary heart disease is estimated to be 5-fold higher with the presence of premature CAC than with traditional risk factors. This vulnerable population is important for initiation of statin therapy for primary prevention regardless of the function of statins to lower cholesterol levels. Young people with CAC >100 have an even higher risk for ASCVD events and all-cause mortality.[17] Therefore, recognizing the presence of CAC with imaging strategies can guide the initiation of therapy in young adults. The optimal age for CAC scanning to assess initiation of statin therapy in men is 37 years, in women without risk age 58 and in women with diabetes age 50.[18]

Traditional risk calculators assessing subclinical atherosclerosis are very common among middle-aged individuals who are considered low to medium risk, and more than 40% of this population has evidence of peripheral plaque development on three-dimensional vascular ultrasonography over the next 3-year interval.[19] These data support early initiation of statin therapy to delay the development of atherosclerosis and reduce the risk of events prior to the development of CAC.

STATINS CAN BE COST EFFECTIVE

Statin therapy for the primary prevention of ASCVD can be cost effective. microsimulation model of US adults aged 45 to 75 years, the current 10-year ASCVD risk threshold (≥7.5% risk threshold) used in the ACC/AHA cholesterol treatment guidelines has an acceptable cost-effectiveness profile (ICER, $37 000/QALY), but more lenient ASCVD thresholds would be optimal using cost-effectiveness thresholds of $100 000/QALY (≥4.0% risk threshold) or $150 000/QALY (≥3.0% risk threshold).[20]

STATINS ARE SAFE, EFFECTIVE, AND WELL TOLERATED FOR THE PRIMARY PREVENTION OF ASCVD

Statins are safe and generally well tolerated. Statin associated side effects (SASE) are muscle pain, myopathy, Rhabdomyolysis, statin-induced autoimmune myopathy, newly diagnosed Diabetes, liver disorder, renal disorder, hemorrhagic stroke, dementia disability, cataracts, cancer, and tendon injuries.[21] The authors critically reviewed evidence from randomized clinical trials, meta-analyses, and observational studies. They reported that the most frequently reported SASE in clinical practice is myalgia (muscle symptoms without elevated creatine kinase [CK]), but the difference in incidence is <1% among statin-treated and placebo-treated patients in randomized clinical trials. The risk of newly diagnosed diabetes is nearly 0.2% per year of treatment and risk of serious hepatotoxicity is <0.01% with all statins.No convincing evidence of causation Statin Use and Risk of Hemorrhagic Stroke, Cognition Elderly patients, cataract or cancer disorders in primary prevention. All this evidence must be weighed as well as the important benefits of statins mentioned above, Observation that statin discontinuation is associated with an increase risk of MI and cardiovascular death in the general population.[22]

The risk of myopathy and rhabdomyolysis with statin therapy is <0.1%, while statin induced autoimmune myopathy is exceedingly rare. There is no convincing evidence of a causal relationship between statin use and the risk of hemorrhagic stroke, cognitive impairment in older patients, cataracts, or cancer in primary prevention. The totality of this evidence should be weighed against the significant benefits of statins as outlined above, as well as the observation that statin discontinuation is associated with an increased risk of MI and cardiovascular death in the general population.[22]

STATINS ARE STILL DEBATED IN OLDER ADULTS

It is well established that statins reduce adverse cardiovascular outcomes but it remains unclear whether this reduction applies to older adults. Although older individuals have the highest absolute risk for atherosclerotic cardiovascular disease (ASCVD) events, the US guidelines for blood pressure and cholesterol recommend lower-intensity, less-aggressive treatment strategies in this high-risk population. The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Cholesterol guidelines, citing the statin-associated reduction in ASCVD morbidity burden in older adults in secondary prevention, recommend ongoing use of statins in this population. However, when addressing primary prevention in older adults (>75 years), the recommendations are less direct and weigh heavily on the patient-physician discussion as well as overall concerns for polypharmacy, frailty, and life-expectancy.

Older adults are likely to be more susceptible to cardiovascular events and are also less tolerant of drug-related side effects compared with younger adults because of age-related decline and increased burdens of disease and the likelihood of being on multiple medications.[23]

The PROSPER trial evaluated the effects of pravastatin in an older adults' population (70-82 years) with and without baseline ASCVD. At 3.2 years mean follow up period, decrease in LDL-C by approximately 34% as well as reductions in myocardial infarction (MI) and coronary deaths were noted in the pravastatin group versus the placebo group.[24] Ridker et al. performed an age-stratified meta-analysis of the JUPITER and HOPE-3 trials and reported 26% relative risk reduction with rosuvastatin therapy among asymptomatic adults older than 70 years.[25]

CONCLUSIONS

Statins are widely recommended for primary prevention of cardiovascular disease Statins are a class of drugs that lower cholesterol by inhibiting the enzyme HMG-CoA reductase.

Appropriate initiation of statin drug therapy during the early stages of atherosclerosis and plaque development is critical to prevent the development of ASCVD. Recognizing the presence of CAC with imaging strategies can guide the initiation of therapy in young adults. The optimal age for CAC scanning to assess initiation of statin therapy in men is 37 years, in women without risk age 58 and in women with diabetes age 50 Statins have pleiotropic effects that protect the cardiovascular system. Primary prevention of ASCVD with statins can save costs. Statins have side effects, but the incidence is very low. The use of statins to prevent ASCVD in the elderly is controversial due to polypharmacy, frailty, and life.

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REFERENCES

1. Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. Health Aff (Millwood). 2007;26(1):38–48.

2. WHO. Cardiovascular Diseases (CVDs) [Internet]. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

3. Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Grusing S, et al. Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Rockville (MD); 2016.

4. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul;63(25 Pt B):2889–934.

5. Marcus ME, Manne-goehler J, Theilmann M, Farzadfar F, Moghaddam SS, Keykhaei M, et al. Articles Use of statins for the prevention of cardiovascular disease in 41 low-income and middle-income countries : a cross- sectional study of nationally representative , individual-level data. :369–79.

6. Cho Y, Jeong Y, Seo DH, Ahn SH, Hong S, Suh YJ, et al. Use of statin for the primary prevention of cardiovascular outcomes in elderly patients: A propensity-matched cohort study. Atherosclerosis. 2021 Jul;328:92–9.

7. Pletcher MJ, Bibbins-Domingo K, Liu K, Sidney S, Lin F, Vittinghoff E, et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Ann Intern Med. 2010 Aug;153(3):137–46.

8. J. SN, C. SS, E. OC, A. RN, Marie NA, S. KS, et al. Managing Atherosclerotic Cardiovascular Risk in Young Adults. J Am Coll Cardiol [Internet]. 2022 Mar 1;79(8):819–36. Available from: https://doi.org/10.1016/j.jacc.2021.12.016

9. Ference BA, Graham I, Tokgozoglu L, Catapano AL. Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series. J Am Coll Cardiol. 2018 Sep;72(10):1141–56.

10. Mehta A, Virani SS, Ayers CR, Sun W, Hoogeveen RC, Rohatgi A, et al. Lipoprotein(a) and Family History Predict Cardiovascular Disease Risk. J Am Coll Cardiol [Internet]. 2020;76(7):781–93. Available from: https://www.sciencedirect.com/science/article/pii/S0735109720357375

11. Peter L, Joseph L, M RP, E. FM, Y. HP, Valentin F, et al. Inflammation, Immunity, and Infection in Atherothrombosis. J Am Coll Cardiol [Internet]. 2018 Oct 23;72(17):2071–81. Available from: https://doi.org/10.1016/j.jacc.2018.08.1043

12. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. 2017;229–43.

13. Razavi A, Mehta A, Sperling L. Statin therapy for the primary prevention of cardiovascular disease: Pros. Atherosclerosis. 2022 Jul 1;356.

14. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015 Oct;66(15):1657–68.

15. Razavi AC, Kelly TN, Budoff MJ, Bazzano LA, He J, Fernandez C, et al. Atherosclerotic cardiovascular disease events among statin eligible individuals with and without long-term healthy arterial aging. Atherosclerosis [Internet]. 2021;326:56–62. Available from: https://www.sciencedirect.com/science/article/pii/S0021915021001398

16. Miedema MD, Dardari ZA, Nasir K, Blankstein R, Knickelbine T, Oberembt S, et al. Association of Coronary Artery Calcium With Long-term, Cause-Specific Mortality Among Young Adults. JAMA Netw Open [Internet]. 2019 Jul 19;2(7):e197440–e197440. Available from: https://doi.org/10.1001/jamanetworkopen.2019.7440

17. Carr JJ, Jacobs DRJ, Terry JG, Shay CM, Sidney S, Liu K, et al. Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death. JAMA Cardiol. 2017 Apr;2(4):391–9.

18. Dzaye O, Razavi AC, Dardari ZA, Shaw LJ, Berman DS, Budoff MJ, et al. Modeling the Recommended Age for Initiating Coronary Artery Calcium Testing Among At-Risk Young Adults. J Am Coll Cardiol [Internet]. 2021;78(16):1573–83. Available from: https://www.sciencedirect.com/science/article/pii/S0735109721059684

19. Beatriz LM, Leticia FF, Belén O, Manuel GRJ, Fátima SC, Héctor B, et al. Short-Term Progression of Multiterritorial Subclinical Atherosclerosis. J Am Coll Cardiol [Internet]. 2020 Apr 14;75(14):1617–27. Available from: https://doi.org/10.1016/j.jacc.2020.02.026

20. Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-Year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. JAMA. 2015 Jul;314(2):142–50.

21. Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, et al. CHOLESTEROL CLINICAL PRACTICE GUIDELINES 2018 AHA / ACC / AACVPR / AAPA / ABC / ACPM / ADA / AGS / APhA / ASPC / NLA / PCNA Guideline on the Management of Blood Cholesterol Association Task Force on Clinical Practice Guidelines. 2019.

22. Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013 Apr;158(7):526–34.

23. Saeed A, Mehta LS. Statin Therapy in Older Adults for Primary

Prevention of Atherosclerotic Cardiovascular Disease: The Balancing Act. Am Coll Cardiol. 2020;

24. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet [Internet]. 2002 Nov 23;360(9346):1623–30. Available from:

https://doi.org/10.1016/S0140-6736(02)11600-X

25. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary Prevention With Statin Therapy in the Elderly: New Meta-Analyses From the   Contemporary JUPITER and HOPE-3 Randomized Trials. Vol. 135, Circulation. United States; 2017. p. 1979–81.