Atherosclerosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Statin therapy for the primary prevention ofatherosclerotic cardiovascular disease: Pros

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ARTICLE INFO

Keywords:
Statin
Atherosclerosis
Primary prevention
Cardiovascular disease

ABSTRACT

The initiation of statins for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) remains a debated subject, despite decades worth of clinical trial data demonstrating efficacy, effectiveness, and safety. Statin therapy, in addition to blood pressure-lowering drugs and efforts to reduce cigarette smoking, was a key component of the preventive cardiology renaissance that achieved a dramatic reduction in ASCVD-related mortality from the 1950s to 2010. However, deaths attributable to ASCVD have increased by approximately 13% in recent years, which are in part driven by incomplete treatment of risk factor burden starting in youth. Statins are a cornerstone of preventive cardiology practice, not only due to their lipid-lowering properties, but also in part due to their ability to exert pleiotropic effects that promote atherosclerotic plaque stability which reduces the likelihood of atherothrombotic clinical events. While the benefit of statin therapy undoubtedly depends on the presence and degree of atherosclerotic plaque burden, a broader statin allocation strategy on a population-based level should be considered especially in younger communities that are disproportionately affected by ASCVD risk factors. Thus, the era of precision medicine must be balanced with a pragmatic, cost-effective approach that maximizes ASCVD prevention across the life course. Herein, we examine the pros of statin pharmacotherapy in primary prevention while examining over three decades worth of basic science, translational, and clinical research in the setting of clinical practice guidelines.

1. Increased use of statins for primary prevention is needed given the recently slowed reduction in ASCVD mortality

Statins (HMG CoA reductase inhibitors) have been used as a foundational preventive pharmacotherapy since the FDA approval on September 1st, 1987 of lovastatin [1]. Millions of primary atherosclerotic cardiovascular disease (ASCVD) events have been prevented since then due to the widespread utilization and evolution of statin therapy [2]. Importantly, implementation of findings from randomized clinical trials [3] has been translated to population-level cholesterol lowering interventions that have achieved reduction in ASCVD events globally, a major public health achievement of the modern medicine era. However, the prevention of ASCVD has stalled over the past decade.

Efforts to decrease tobacco use in addition to improvements in blood pressure and cholesterol management led to a nearly 30% reduction in ASCVD mortality from the 1950s through 2010(2). In contrast, since 2010 the reduction in ASCVD mortality has slowed to 1.4%. Additionally, deaths attributable to ASCVD have also increased by approximately 13% since 2008 [4–6]. While the mechanisms justifying these trends are likely multifactorial, increasing ASCVD event rates in younger adults are perhaps one of the most significant contributors to the stagnation in event reduction [7,8].

2. Statins for primary prevention can impact cardiovascular risk across the life course: targeting hypercholesterolemia at a young age and the concept of cholesterol-exposure years

Nearly all individuals who experience premature ASCVD events have underlying modifiable cardiovascular risk factors including tobacco use, hypercholesterolemia, hypertension, and/or type 2 diabetes. In the INTERHEART study (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) nine traditional ASCVD risk factors were responsible for 90–94% of the population attributable risk (PAR) for myocardial infarction, with a larger PAR reported in younger adults [9]. The prevalence of dyslipidemia is particularly high in young adulthood with less than 15% of young adults

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https://doi.org/10.1016/j.atherosclerosis.2022.07.004
Received 11 June 2022; Received in revised form 1 July 2022; Accepted 6 July 2022
Available online 14 July 2022
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maintaining time-weighted average lipid values considered normal or optimal (LDL-cholesterol <100 mg/dL, HDL-cholesterol >60 mg/dL, triglycerides <150 mg/dL) [10,11]. Statin therapy should be considered for adolescents and young adults between 10 and 39 years of age when LDL-cholesterol values are high (≥160 mg/dL) and recommended when very high (≥190 mg/dL) [11,12]. The pharmacological treatment of hypercholesterolemia has changed over the past 20 years given randomized clinical placebo-controlled trial data for statin utilization in children [13]. A meta-analysis of randomized clinical trials of statin utilization in children with familial hypercholesterolemia has demonstrated 30% LDL-cholesterol reduction with no significant differences in adverse events, including muscle or liver toxicity, or Tanner staging when comparing statins versus placebo [14,15].

In addition to targeting treatment of hypercholesterolemia, reduction in cumulative exposure to LDL-cholesterol and its time-weighted average value is an important goal. Intravascular ultrasound studies have consistently demonstrated that atherosclerotic plaque progression is directly proportion to absolute plasma LDL-cholesterol values [16]. Conceptually, an individual's total atherosclerotic plaque burden can in part be approximated by their biological age x mean LDL-cholesterol to obtain a composite measure of mg/dL exposure years (Fig. 1). Assuming that the mean untreated LDL-cholesterol in the United States is 125 mg/dL, the minimum threshold of cholesterol-years necessary to produce large enough plaque to increase the risk of myocardial infarction is estimated to be 5,000 mg/dL-years (125 mg/dL x 40 years). Past this threshold, the risk of myocardial infarction appears to double with each decade of exposure to the same LDL-cholesterol concentration [16,17] which supports the utilization of statin therapy as early as possible, in addition to appropriate lifestyle modification, for individuals at risk.

The concept of cholesterol exposure years demonstrates that the timing of initiating lipid-lowering pharmacotherapy with statins is exceedingly important for the prevention of ASCVD events. Lowering LDL-cholesterol from 125 mg/dL (the mean untreated LDL-C level in the United States) to 70 mg/dL before 40 years of age could reduce the risk of myocardial infarction and halt atherosclerotic plaque progression. By age 40, the risk of myocardial infarction is 1% after exposure to 5,000 mg-years of LDL-C and doubles thereafter each decade for unchanged plasma LDL-C levels [16]. On the other hand, waiting to initiate statin therapy at age 40 years for an individual with an average LDL-cholesterol of 130 mg/dL would mean that this person is likely to harbor a significant burden of atherosclerotic plaque that might be prone to rupture [16]. Thus, timely initiation of statin therapy during the early stages of atherosclerosis and plaque development is

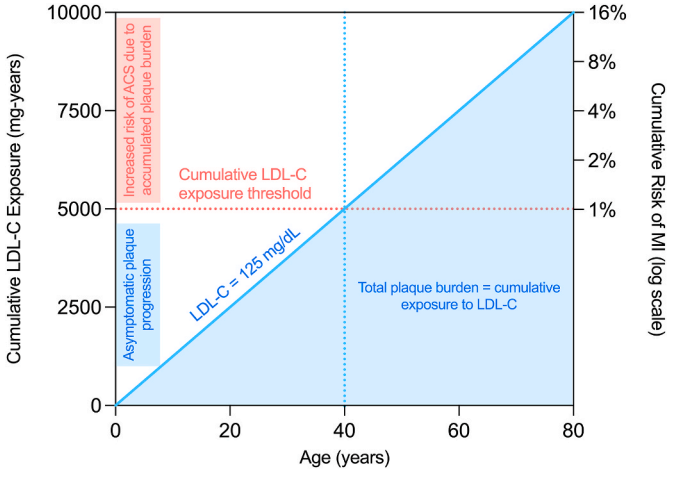

Fig. 1. Concept of cumulative LDL-cholesterol exposure threshold in relation to total plaque burden and risk of ASCVD events.
Adapted from Ference et al. "Impact of Lipids on Cardiovascular Health: JACC Promotion Series".

fundamental to preventing ASCVD events. Current guidelines in adults endorse statin pharmacotherapy in high-risk primary prevention populations, including those with familial hypercholesterolemia, LDL-C ≥190 mg/dL, type 2 diabetes, 10-year ASCVD risk ≥20%, and/or those with a 10-year risk ASCVD risk between 5 and 20% with multiple risk enhancing factors [18]. Emerging data has shown a synergistic relationship between risk enhancing factors themselves, for example between elevated lipoprotein(a) and a family history of premature ASCVD [19], which may favor statin pharmacotherapy initiation earlier than the traditional 40 year age cut-point used in the Pooled Cohort Equations 10-year ASCVD risk estimation.

3. Statins prevent cardiovascular events through pleiotropic effects

Atherothrombosis leads to clinical ASCVD events and involves a complex interaction between atherosclerotic plaque, dysfunctional vascular endothelium, oxidized lipoproteins, inflammation, and platelet reactivity [20]. It has been postulated that the cardioprotective benefits of statins are in part related to pleiotropic effects that are independent of LDL-cholesterol lowering [21]. Evidence suggests that statins impact both innate and adaptive immune responses by decreasing production of inflammatory cytokines, cellular adhesion molecules, and reactive oxygen species [22]. Statins also alter the expression of nitric oxide synthase in the endothelium and decrease platelet reactivity which promote atherosclerotic plaque stability [23,24]. However, the contribution of these pleiotropic effects to improved clinical outcomes in primary prevention has not been rigorously quantified.

4. An atherosclerosis-based approach to the initiation of statin therapy can improve precision primary prevention

Atherosclerosis is a chronic disease that begins at a young age; however, a radiological threshold to initiate statin therapy to simultaneously preserve both efficacy and precision needs further investigation. Observations from the Bogalusa Heart Study [25] and Pathobiological Determinants of Atherosclerosis in Youth Study [26] in particular have demonstrated that fatty streaks begin as early as two years of age and are strongly associated with nearly all traditional risk factors, including total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, body mass index, and smoking. The natural progression of fatty streaks ensues with development of intermediate lesions and atheromas which are soft plaques that ultimately progress towards a fibrotic and/or calcified composition [27]. Characterization of atherosclerotic plaques utilizing imaging techniques including vascular ultrasound and non-contrast computed tomography is an important tool for clinical decision making as evidence suggests significant differences in treatment benefit among statin eligible candidates with or without vascular calcification [28,29]. The number needed to treat with statins to prevent one ASCVD event is approximately two-fold higher for individuals with coronary artery calcium (CAC) versus those who maintain long-term absence of CAC [30].

While calcification has been thought to represent one of the late stages of atherosclerosis, findings have demonstrated that between 10 and 34% of young adults have evidence of CAC by as early as 32 years of age [31,32]. Premature CAC is associated with an approximate 5-fold higher risk of coronary heart disease events beyond traditional risk factors [32] suggesting that early initiation of statin therapy in this vulnerable population is important for primary prevention regardless of cholesterol levels. Young people with CAC >100 have an even higher risk for ASCVD events and all-cause mortality [31,32]. Therefore, an evidence-based CAC scanning approach can complement and guide the early initiation of statin therapy in young adults. Assuming a number needed to scan to detect premature CAC of 4, the optimal age to consider a first CAC scan that may be able to guide initiation of statin therapy would be 37 years in men and 50 years in women with diabetes, and 42

years in men and 58 years in women without risk factors [33].

While the selective utilization of statins according to the presence versus absence of CAC [29,34,35] is beneficial on an individual level, a broader approach may be valuable to primary prevention efforts on a population level (Table 1). For example, precision in statin allocation may be improved by the presence versus absence of carotid plaque [36] as well as thoracic aortic calcification [37], which may be more prevalent in younger populations and women compared to older persons and men, respectively. The Progression of Early Subclinical Atherosclerosis (PESA) study has shown that subclinical atherosclerosis is highly prevalent among middle-aged individuals deemed to be low-to-intermediate risk by traditional risk calculators, and that more than 40% of this population has evidence of peripheral plaque progression on three-dimensional vascular ultrasound within a 3-year follow up interval [38]. These data support earlier initiation of statin therapy to delay progression of atherosclerosis and reduce the risk of incident events prior to the development of CAC.

5. Statins for the primary prevention of ASCVD can be cost effective

Statin therapy for the primary prevention of ASCVD can be cost effective. The cost effectiveness of statin initiation based on 10-year ASCVD risk predicted using the American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equations has been evaluated using a cardiovascular disease microsimulation model based on data from the National Health and Nutrition Examination Surveys [39]. Pandya et al. have demonstrated that the 10-year ASCVD risk threshold ≥7.5% (intermediate and high-risk categories) has an acceptable cost-effectiveness profile (incremental cost-effectiveness ratio $37,000 per quality-adjusted life-year) among US adults aged 45–75 years. More recently, Kohli-Lynch and colleagues used a cardiovascular disease policy model and reported that using a lower 10-year ASCVD risk threshold ≥5% (borderline, intermediate and high-risk categories) and expanding statin use for primary prevention would also be cost-effective ((incremental cost-effectiveness ratio $33,558 per quality-adjusted life-year) and would prevent the most ASCVD events [40].

6. Statin are safe, effective, and well tolerated

Statins are safe and generally well tolerated. Statin associated side effects (SASE) is an umbrella term that encompasses myalgia, myopathy, rhabdomyolysis, statin induced autoimmune myopathy, newly diagnosed diabetes, liver injury, renal injury, hemorrhagic stroke, cognitive impairment, cataract, cancer, and tendon injury [11]. It is estimated that almost 10% patients in clinical practice discontinue statins due to a SASE or because of the fear of developing a SASE(41). The issue of statin safety and SASE was recently evaluated in a scientific statement from the American Heart Association [42]. The authors critically reviewed evidence from randomized clinical trials, meta-analyses, and observational studies. They reported that myalgia (muscle symptoms without elevated creatine kinase [CK]) is the most frequently reported SASE in clinical practice, but the difference in incidence is <1% among statin-treated and placebo-treated patients in randomized clinical trials. The risk of myopathy and rhabdomyolysis with statin therapy is <0.1%, while statin induced autoimmune myopathy is exceedingly rare. Importantly, myopathy and rhabdomyolysis are encountered most frequently in the setting of drug interactions (e.g. concomitant gemfibrozil, CYP450 inhibitor use). 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. There is no convincing evidence demonstrating a causal relationship between statin use and risk of hemorrhagic stroke, cognitive impairment in older patients, cataract, or cancer in the primary prevention setting. 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 [41].

7. Statins in older adults

Statin therapy for primary ASCVD prevention in older adults is a disputed issue [43]. Aging is the strongest risk factor for incident nonfatal and fatal ASCVD events, however older adults are at higher risk for SASE due to frailty, slower hepatic and/or renal metabolism, and polypharmacy. The PROSPER trial demonstrated that pravastatin use in adults aged 70–82 years decreased the risk of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke by 15% [44]. However, this reduction in risk was driven primarily by a reduction in events in the secondary prevention population of the trial. A post-hoc secondary analysis of the lipid lowering therapy (LLT) arm of ALLHAT trial demonstrated no reduction in all-cause mortality with pravastatin [45]. In contrast, 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 [46]. More recently, an individual participant meta-analysis from the Cholesterol Treatment Trialists' Collaboration revealed a 13% relative risk reduction in age group 70–75 years, although no significant risk reduction in age group >75 years with 1 mmol/L reduction in LDL-cholesterol with statin or more intense statin

Table 1
Initiation of statin therapy according to subclinical atherosclerotic burden.

Subclinical Atherosclerosis	Imaging Modality	Pros	Cons
Coronary Artery Calcium	Non-Contrast CT	- Standardized measurement and scoring via the Agatston method - Most strongly associated with atherosclerotic cardiovascular disease outcomes among all forms of subclinical atherosclerosis	- Vascular calcification is traditionally a later stage manifestation of atherosclerosis - Less prevalent among women, especially in young age - Not as robust for stroke prediction
Coronary Plaque	Coronary CTA	- More comprehensive assessment of coronary atherosclerosis, including lumen stenosis, plaque volume, number of involved coronary segments, presence of high-risk plaque features	- No universal coronary CTA score that comprehensively combines all plaque features - More invasive and requires intravenous contrast
Thoracic Aortic Calcium	Non-Contrast CT	- Standardized measurement and scoring via the Agatston method - Strongly associated with incident stroke - May develop prior to coronary artery calcium, permitting earlier initiation of statin therapy	- Population-based percentile data have yet to be defined
Carotid Plaque	Ultrasound	- No radiation - Closely associated with stroke outcomes - Likely to develop prior to coronary and/or thoracic aortic calcification	- No standardized carotid plaque burden score - Less useful for coronary heart disease prediction - User-dependent
Ileo-Femoral Plaque	Ultrasound	- Most prevalent vascular territory affected among both men and women	- Not as robustly studied with respect to prospective atherosclerotic cardiovascular disease outcomes

CT = computed tomography; CTA = computed tomography angiography.

therapy as compared with placebo or less intensive therapy was observed in the primary prevention setting [47]. Two trials STAREE (age ≥70 years; NCT02099123) and PREVENTABLE (age ≥75 years; NCT04262206) are actively recruiting older adults to study the benefits and risks of atorvastatin therapy in the primary prevention setting. The results of these large contemporary trials will be instrumental in providing more definitive evidence regarding statin use in older adults.

8. Conclusions

For over 30 years statin therapy has stood the test of time to remain the cornerstone of preventive cardiology practice and ASCVD risk reduction. The degree of ASCVD risk reduction with statins is dependent on baseline risk and directly proportional to percentage of LDL-cholesterol lowering; however, statins also have broader pleiotropic effects that stabilize atherosclerotic plaque. Moreover, the benefit of statin therapy also depends on the presence and degree of atherosclerotic plaque burden, as the number needed to treat to prevent one ASCVD event is at least two-fold higher for individuals without CAC versus those with prevalent CAC. Yet, previous clinical trials involving statins had a heterogenous composition of individuals across the spectrum of plaque burden, therefore the relative and absolute risk reduction attributable to statin therapy is likely underestimated compared to modern efforts aimed at enrolling individuals according to the presence versus absence of significant plaque burden. While atherosclerotic plaque imaging has ushered in a new era of precision medicine for statin pharmacotherapy, we must balance these efforts with a pragmatic, cost-effective approach to maximize the lifetime prevention of ASCVD in both affluent and underserved communities across the globe starting from a young age.

Author contributions

Alexander C. Razavi: investigation, methodology, validation, writing original draft, critical reviewing and editing final draft.

Anurag Mehta: investigation, methodology, validation, writing original draft, critical reviewing and editing final draft.

Laurence S. Sperling: investigation, methodology, validation, writing original draft, critical reviewing and editing final draft.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Dr. Paolo Raggi and the *Atherosclerosis* journal team for the invitation to present, discuss, and review research related to statin therapy in the primary prevention of atherosclerotic cardiovascular disease.

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