

A Critical Evaluation of the Role of Routine Uses of Statin as a Tool for Primary Prevention of Cardiovascular Diseases

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Abstract

Use of Statin is a cornerstone in modern day medical practice and an essential component for primary prevention of cardiovascular diseases (CVD). Various evidences exemplify and resonate the importance of Statins in reducing CVD mortality and improvement of survivability. However, there is a continental variation in recent guidelines directing lipid-lowering therapy in regards to aim, dose, timing as well as the protocol for initiation of therapy. Similar uncertainties exist with regards to the generalizability of the finding from available evidence, a variation of benefits of Statin with respect to age and gender, the validity of the research conducted and actual gain in survivability and mortality benefits. Thus, there is a need for looking at the actual indications, risk-benefit ratios and cost effectiveness before tediously prescribing Statin for the primary prevention of CVDs. This paper will attempt to critically review the evidence behind the uses of Statins in the primary prevention of CVDs.

Keywords

Statin, Cholesterol, Cardiovascular Diseases, Primary Prevention

1. Introduction

CVDs are a spectrum of disorder affecting the heart or the blood vessels and sharing a common set of risk factors. These are the number one leading the cause of death globally with estimated 30% or 17.3 million deaths in

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2008 with a projection to increase to 23.3 million by 2030 [1]. 80% of the deaths occur in low to middle-income countries. It is postulated that about 40.5% of the US population will suffer from some forms of CVD with subsequent 61% increase in total health care cost related to CVD by 2030 [2]. The gravity of the situation is reflected in developed countries as well. Heart diseases account for about half of all deaths in the European region and 1 in every 4 deaths in the US resulting in approximately \$108.9 billion healthcare cost annually [3]. These facts point towards the need for global action against CVDs and more specifically promotion of preventive approaches with a goal targeted at CVD risk reduction [4]. LDL cholesterol, along with hypertension, smoking and abdominal obesity are the key CVD risk factors [3]. Worldwide about one-third of all ischemic heart diseases are attributable to high cholesterol [5]. In view of the fact that 1% decrease in cholesterol level could lead to a 2% - 4% decrease in CVD mortality, there has been various ongoing global initiatives and guidelines focusing on the reduction of cholesterol through diet and pharmacotherapy [6]. Various observational studies and randomized controlled trials (RCTs) have demonstrated that Statin medications are the most effective and number one choice for cholesterol lowering pharmacotherapy [7]. Since the inception of statin therapy, there have been paradigm shifts in the guideline and evidence for the use of Statins in CVD risk reduction.

1.1. Statin

Statins are the commonly prescribed lipid-lowering agent. The chemical structures of statins include an enzyme substrate, complex hydrophobic ring and side groups. Currently, there are about seven Food & Drug Administration (FDA) approved Statins in the market, including Atorvastatin, Lovastatin, Fluvastatin, Pravastatin, Simvastatin, Rosuvastatin and Pitavastatin; differentiated based on origin (fungal-derived vs synthetic), solubility (lipophilic vs hydrophilic), affinity for target enzymes and entry into the liver [8] [9]. Rosuvastatin is the most potent statin with respect to lipid lowering followed by Atorvastatin, Simvastatin and Pravastatin. Pitavastatin is the most effective statin with fewer side effects and drug interaction [9]. Statins are HMG-CoA reductase inhibitor, which enters into the hepatocytes either through passive diffusion or organic anion transport and competitively bind and inhibits the HMG-CoA reductase in the hepatic cells with resultant blockage of the forward pathways for cholesterol synthesis (**Figure 1**) [9]. This, on one hand, directly inhibits new cholesterol synthesis and indirectly results in a compensatory increase in the LDL receptors on the hepatic cells with increased intake of VLDL and LDL into the hepatocytes and subsequent excretion through bile salt [9]. Both the mechanisms translate into the reduction of plasma cholesterol. Various imaging trials have shown that Statins had a greater effect on atherosclerotic plaque stabilization, regression and reduction of vascular stiffness if given early in the course of the disease through changes in the level of inflammation, lipid core & fibrosis [10]-[12]. In spite of some drug-to-drug variability, Statins are usually relatively safe. Most common side effects include a headache, myopathy, dizziness, nausea/vomiting and abdominal cramp [13]. FDA is currently advising consumers regarding few other potential side effects of Statin, including Type 2 Diabetes Mellitus (DM), cognitive impairment and myopathy [14].

1.2. History of Statin

The lipid-lowering drug discovery convened through periods of controversies, discovery and trials before reaching the current stage. Though there were occasional reporting of the link between plasma cholesterol and CVD but it was not until the 1950s and 1960s when it became apparent that elevated plasma cholesterol was a major risk factor for CVD through the Framingham and Seven countries study [15] [16]. This resulted in a whole new horizon of cholesterol-lowering drug discovery and controlled trials. But due to lack of clear evidence and pathophysiological knowledge related to the benefit of cholesterol lowering, it remained a controversy for years before the discovery of lovastatin, a potent HMG-CoA reductase inhibitor in the 1980s. However, what seemed like a potential success story was again jarred by interruption of the clinical trial following the report of animal toxicity [15]. Thereafter, after much deliberation, a trial was restarted for lovastatin in 1983 and by 1987 lovastatin was approved by the US FDA advisory council. This was the beginning of the clinical journey of the Statins with the development of other Statins between 1988 and 2003 [15]. There was a surge of Statin from 2007 onwards with a heterogeneous use of Statins among various medical practices [17].

2. Current Guidelines

Over the years, there were various guidelines including the European Society of Cardiology/European

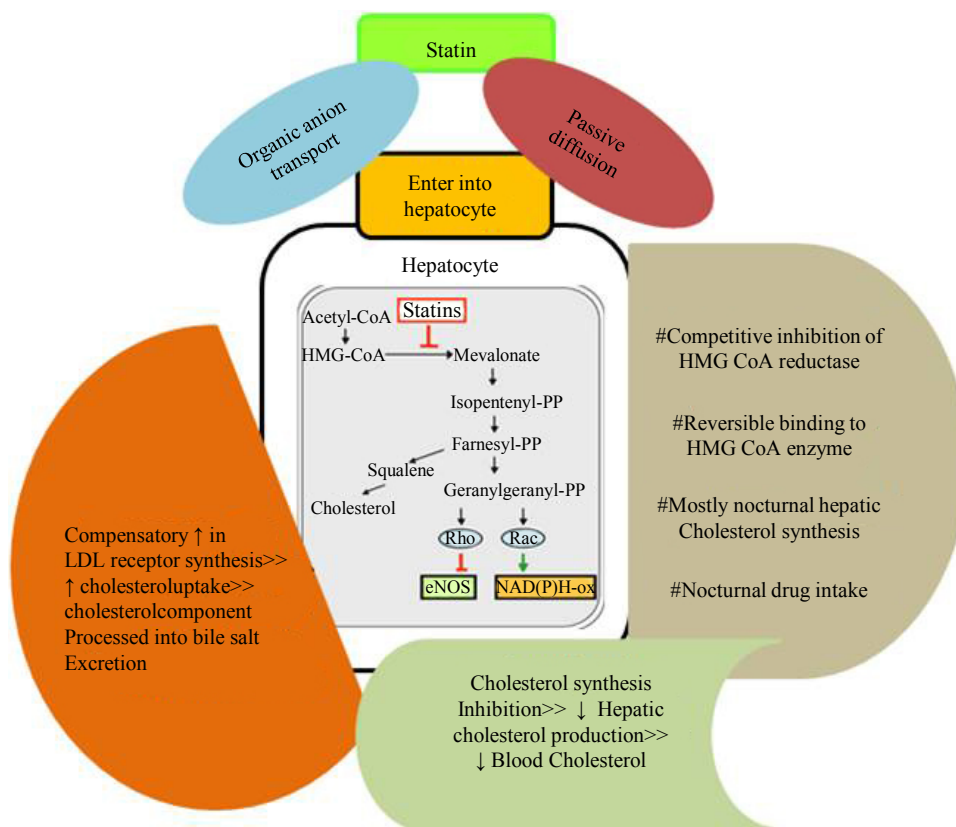


Figure 1. Mechanism of action of Statins.

Atherosclerosis Society (ESC/EAS) and American Heart Association/American College of Cardiology (AHA/ACC) guideline, which characterized the treatment protocol with statins. For this write up we will be focusing on the recent guidelines especially the **ESC/EAS** guideline of 2011 and the **AHA/ACC** guideline of 2013 for the use of statin in the primary prevention of cardiovascular diseases. The **ESC/EAS** guideline promotes therapeutic intervention based on the CVD risk stratification using SCORE system estimating the 10-year risk of CV death [18]. ‘SCORE’ system classifies those without CVD risk into three categories; high risk ($\geq 5\%$ and $< 10\%$ 10 year CVD risk); moderate risk ($\geq 1\%$ and $< 5\%$ 10-year risk along with other risk factors) and low risk ($< 1\%$) [18]. The overall target of therapy is an absolute reduction of LDL cholesterol < 1.8 mmol/L or at least 50% reduction of LDL cholesterol to provide the best benefit in CVD risk reduction [18].

Later on in 2013, **AHA/ACC** put forth the most recent guideline recommending fixed-dose strategies rather than target goal to reduce LDL-cholesterol. The new guideline focuses on the reduction of total good cholesterol using various intensities of statin therapy as determined exclusively through controlled trials. The evidence was particularly effective for 4 patient groups including primary prevention of cardiac diseases in patients aged 40 - 75 years with an estimated 10 years atherosclerotic cardiovascular disease (ASCVD) $\geq 7.5\%$ and 40 to 75 years diabetic patients with LDL level between 70 to 189 mg/dl [19] [20].

The risk assessment for this guideline was done using a new pooled cohort risk estimator developed from 5 NHLBI-sponsored population-based cohort. The statin therapy was classified based on dose into high, moderate and low-intensity statin. There is no specific LDL cholesterol goal but specifies the need for dose adjustment once LDL cholesterol is < 40 mg/dl.

Both the guidelines actually more or less complement each other. With a fundamental difference that ESC/EAS guideline recommends statin therapy based on CVD risk stratification and LDL level ≥ 2.5 mmol/L, whereas ACC/AHA guideline call for primary prevention in an advent of 10-year ASCVD risk of 7.5% irrespective of LDL-cholesterol. The basic treatment guideline for initiation of statin in primary prevention of ASCVD as per both guidelines is given below [19].

- ❖ For primary prevention with LDL > 4.9 mmol/L

- **ESC/EAS:** Target LDL < 2.5 mmol/L
- **AHA/ACC:** High-intensity statin therapy until at least 50% reduction of LDL cholesterol
- ❖ Primary prevention in those with diabetes
- **ESC/EAS:** Target ≤ 1.8 mmol/l (complicated diabetes) and < 2.5 mmol/l (uncomplicated DM)
- **AHA/ACC:** High-intensity statin in high risk diabetics and moderate intensity statin in low intensity statin
- ❖ Primary prevention in high-risk
- **ESC/EAS:** Target LDL < 1.5 mmol/L
- **AHA/ACC:** 5% to 7.5% risk for CVD (Moderate intensity statin therapy) vs >7.5% risk for CVD (moderate to high-intensity statin therapy)

Various studies looking at the effectiveness of the two guidelines found that the desired reduction of the LDL cholesterol was found in 21%, 44% and 62% among very high, high and moderate risk groups under **ESC/EAS** guideline compared to 47% in patients on high-intensity statin therapy as per **ACC/AHA** guideline [19] [21].

3. Supporting Evidence

The *ESC/EAS guideline* is based on the report of meta-analyses done between 2008 and 2012 namely those done by Brugts J.J. *et al.* in 2009; Edward J. Mills *et al.* in 2008; Fiona Taylor *et al.* in 2012 and Trialist in 2012 [22]-[24]. The meta-analyses looked at various randomized controlled trials (RCTs) to determine the effect of different statins on single or a composite CVD effect as given in **Table 1**.

The current *ACC/AHA guideline* is based on a systemic review of RCTS with ASCVD outcomes with the exclusion of observational studies and studies less than 18 months follow-up. Only those RCTS with hard ASCVD outcomes (MI, stroke, CVD deaths published between January 1995 through December 2009 were included in the guideline with provision to consider articles published after 2009 but before the Expert panel deliberation. 6 RCTS namely MEGA, ASPEN, AFCAPS, JUPITER, CARDS and AURORA [25]-[30]. These RCTS were compared either between fixed doses of the statin with placebo or untreated controls or between high or moderate intensity statins. **Table 2** provides the evidence table for this guideline.

Most of the supporting meta-analyses and clinical trials provide strong support to the notion of a relative protective effect of statin in CVD events and mortality. In line with that, CTT trial has found increased benefit of statins over harm especially for subjects in 5% to <10% major cardiovascular disease risk category on high-intensity statin therapy [31]. There is also about 10% reduction in CVD-related mortality in patients on primary prevention statin therapy [31]. The excess risk of serious myopathy, hemorrhagic stroke & DM has been found to be 0.6, 0.5 and 5 per 1000 statin-treated subjects over 5 years period [32]. Some school of thought focused on the legacy effects of statin and emphasized on the post-treatment relation of statin effect up to 8 to 11 years [33]. Also, the cost-effectiveness of the statins along with availability in generic form definitely supports the idea of prolonging statin therapy [34]. National Health and Nutrition Survey data (US NHANES) survey data revealed that even slight decrease in LDL level following statin therapy was associated with prevention of 40,020 deaths, 61,074 Acute MI-related hospitalizations, 22,272 Stroke related hospitalizations with resultant reduction of health care cost through \$440 million [35]. All these characterize the need for initiation of statin early for the primary prevention.

4. Discussion

A detailed exploration of the evidence defining the current guidelines reveal an interplay of evidence supporting the current concept with a rim of following uncertainties regarding the validity and generalizability of the evidence put forward.

Non-uniformity of clinical trials in outcome selection. Most of the clinical trials are heterogeneous in how they classify the CVDs in terms of single output versus composite CVD index, which may actually not be competent for comparison or pooling of trials [22] [24]. Some trials included prevalent CVD cases (<50% versus none), which might result in spurious association [22].

Power. The trials, which included CVDs as secondary response variable may actually be unpowered to look at the effect of statin on CVD outcome.

Generalizability. Most of the trials include and compare the efficacy of statin for a specific group and age range of the population. But there is a need to include the various other groups including more female population,

Table 1. Evidence table for ESC/EAS guideline 2011 [23]-[25].

Meta-analysis Author/ Year	No of trial included	Trial type	Total Popul DM (%)	Gender (M:F)	Age (Range) Age (Mean)	Follow-up (yr.)	Mean Base-line Cholesterol (mmol/l)	End-point	Statin used (No. of trials)	Result
Brugts JJ <i>et al.</i> 2009	10	9 RCT double blind placebo control trials, 1 RCT controlled trial	70,388 23%	66:34	40 - 80 63 yr	4.1	3.63	Major coronary events (death from CHD, nonfatal MI) 0.70 (0.61 - 0.81)	Atorvastatin (3) Simvastatin (1) Lovastatin (1) Pravastatin (4) Rosuvastatin (1)	Significant reduction of all-cause mortality & major coronary events, No big heterogeneity statin therapy with 30% risk reduction, No difference by diabetes status
Edward J Mills <i>et al.</i> 2008	20	RCT w/blinding	63,899 DM in 2 Studies 100%, 2 Studies 0%, Rest 1% - 34%	Female in 4 studies 0%, 1 study 81.1%, Others 15% - 68%	50 - 75 60 yr	3.8	7.75	All cause mortality, CVD mortality, Fatal MI, Nonfatal MI, Major coronary event	Atorvastatin (4) Fluvastatin (3) Lovastatin (2) Pravastatin (11) Atorvastatin (1) Simvastatin (1)	For 17 trials looking for effect of statin on major CVD events & MI found RR 0.85 (0.77 - 0.95) & 0.77 (0.63 - 0.95) respectively. Overall lovastatin better for both prevention of all-cause & CVD mortality followed by Atorvastatin. No significant increase in stroke. Benefits not very w/DM
Fiona Taylor <i>et al.</i> 2012	14	RCTs with Placebo/usual care trial	34,272 DM includes in 4 trials	65:9:34:1	28 - 80 57 yr	1 - 5.3	5 - 6.9	All-cause death, fatal/nonfatal CHD	Atorvastatin (1) Simvastatin (1) Lovastatin (2) Pravastatin (9) Fluvastatin (2)	Combined fatal/nonfatal CVD; RR 0.70 (0.61 - 0.75), No significant evidence of harm or side effect
Cholesterol treatment trialists (CTT)	12	RCTs placebo/usual care trials	- DM 7 - 44	Female 14% - 54%	59 - 66 yr	2.4 - 5.1	3.7	Major coronary events, stroke, revascularization	-	CVD events decreased by 21% per 1mmol/l LDL reduction; a small side effect of myopathy, hemorrhagic stroke

Table 2. Evidence table for ACC/AHA guideline 2013 [26]-[31].

Name of trial	Start Year Site	Participants	Arms		Primary Endpoint	Mean Follow-up	Blinding	Result	Conclusion
			Intervention	Control					
MEGA study	1994; Japan	7832 participants (3966 intervention vs. 3866 control); Age: 40 - 70 years; Female: 68.4%	Diet + Pravastatin (20 to 40 mg)	Diet	First occurrence of coronary event (fatal and non-fatal), Angina, cardiac and sudden death and coronary revascularization procedure	5.3 years	Yes	There was a larger reduction of mean cholesterol (11.5 vs. 2.5); LDL-c (18% vs. 3.2%) and coronary heart disease (HR = 0.67) between intervention and control arm	Lower dose of Pravastatin has similar effect as high dose Pravastatin
AFCAPS trial	1990; US	6605 men and women (3304 intervention and 3301 control); Age: 45 - 73 years; Female: 15%	Lovastatin (20 to 40 mg) + diet	Placebo + diet	First occurrence of coronary event, fatal nonfatal MI, unstable angina and sudden cardiac death	5.2 years	Yes	Lovastatin reduces MI (RR = 0.60), unstable angina (RR = 0.68), coronary events (RR = 0.75) and LDL cholesterol by 25%	Lovastatin reduces the risk first acute major coronary events
ASPEN trial	1999; US	2410 men and women with type 2 Diabetes (1211 Atorvastatin and 1199 placebo); Age: 40 - 75 years; Female: 38%	Atorvastatin (10 mg)	Placebo	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, revascularization, coronary artery bypass surgery, resuscitated cardiac arrest and worsening or unstable angina	4.25 years	Yes	Composite endpoints were not statistically significantly different in Atorvastatin arm compared to placebo, 13.7% vs. 15% respectively	This study did not show any benefit of Atorvastatin in the prevention of coronary diseases in diabetic patients
JUPITER trial	2003; US	15,548 men and women; Age: 60 - 71 yrs; Female: 37% - 39%	Rosuvastatin (20 mg)	Placebo	Non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularization, or cardiovascular death	1.9 years	Yes	Rosuvastatin treated patients who achieved LDL cholesterol less than 1.8 mmol/L had a 55% reduction in vascular events	Reduction in LDL cholesterol was an indicator of successful treatment with Rosuvastatin
CARDS trial	1997; UK	2838 men and women with type 2 Diabetes; Age: 40 - 75; Female: 32%	Atorvastatin (10 mg)	Placebo	Time to first occurrence of the following: acute coronary heart disease events, coronary revascularization, or stroke	3.9 years	Yes	Reduction of acute coronary heart disease by 36%, coronary revascularization by 31% and rate of stroke by 48%	Atorvastatin is effective in reducing the risk of first cardiovascular disease events in patients with type 2 diabetes without high LDL-cholesterol
AURORA trial	2003; International	2276 patients undergoing maintenance hemodialysis; Age: 50 - 80 years; Female: 37%	Rosuvastatin (10 mg)	Placebo	Primary end points were death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	3.8 years	Yes	No significant hazard ratio of 0.96 for the association between Rosuvastatin and combined endpoints compared to placebo. Rosuvastatin did not have any effect on an individual component of the primary endpoint	Though Rosuvastatin reduces LDL in hemodialysis patients but there was no significant effect on the primary cardiovascular endpoints

patients <40 or >75 years of age, various racial and ethnic groups and groups with comorbidities like HIV, inflammatory diseases and organ transplantations [20].

Internal validity. There is little evidence about whether strict research protocol was followed and biases looked at. No effort was seen to reduce bias effect. Many of the trials have pharmaceutical industry sponsorship, which might play a role to bias the result towards statin efficacy. Publication bias may also play a vital role in the reporting from various meta-analyses [22] [24].

Risk-benefit ratio. Not all aspects of tolerability and risk of statin use especially risk on prolong exposure has not been looked into. Also, the comparative efficacies of various individual statins need to be looked at through head-to-head trials with each other and other preventive agents like Aspirin or Clopidogrel. More RCTs are needed for the more detailed look at the risk & benefits of different statins.

Statin is an established drug with potential to reduce all-cause mortality in patients with known cardiovascular disease (CVD). However, there is no such clear-cut indication of similar effect among primary prevention set up. Various trials and meta-analyses in this regard are either inconclusive or lack generalization with only a few finding modest beneficial effect in highly selective patients with high-risk CVD or in combination with other primary prevention techniques [27] [36]-[40]. Thus, there is a need for careful extrapolation of the potential benefit of statins in primary prevention of CVD, especially in low-risk patients. In contrast to the previous notion, therapeutic doses of statin are also associated with some dose-related adverse effects. Though statins are relatively safe and well tolerated but some studies project that the inhibition of production of Mevalonate derivatives may result in potential adverse effect related to Statin use [41]. All trials related to Statin or any other drugs are conducted in highly screened and relatively controlled environment for a short period of time. Thus, the side effects were seen in the general population for prolong use might be more intense and needs to be better studied [41]. There is also a significant risk of drug-related adverse effect associated with pharmacological interaction with other medications especially in patients with high-risk factors and those who are on multiple medications [42]. Also, as per recent FDA report, there is a small but real increased risk of type 2 diabetes mellitus in patients receiving statin [39]. According to Hajar *et al.* the benefit of preventing CVD in patients taking the statin is 2 per 100 compared to 1 in every 200 at risk for the development of type 2 diabetes. Again, using the formula for mean survival calculation, it can be seen that the mean lifetime increase in survival in patients on Statin as seen in various trials will only be around few weeks to few months which raises the question about the true need for such huge investment for the use of statin as a modality for primary prevention of CVD [43]. In a different note, the most commonly used statin in primary prevention is Atorvastatin. Though there are some trials showing a modest survival benefit for other statins but there is no such trial for Atorvastatin. With billions of People using relatively less tested statin worldwide, there is a significant risk of development of various previously unprecedented adverse effects and hence complicating the already overburdened CVD statistics worldwide. Thus, there is a need for a careful weighing of evidence for and against statin therapy and more goal-directed specific research for prolong period with more validity, generalizability and comprehensiveness in an attempt to justify the use of statin as a mode of primary prevention of DVC worldwide. Till then the use of a statin for primary prevention should be more selective, for the specific group of people based on proper screening, risk benefit-ratio and cost-effectiveness.

5. Conclusion

Though current guidelines and supporting evidence give us a sneak peak of the role of statin in the primary prevention of CVD, further research is needed to get the complex picture. There is a need for the use of clinical judgment for individualizing therapies for patients through guided patient-physician discussion weighing in the risk-benefit ratio, insurance status, health resource utilization, risk stratification and informed patient preferences. Further evidence generating trials are needed for more clinical guidance and focus might be put on the legacy effect of statins.

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