Statin

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The Use of Statins in Primary Prevention of Cardiovascular Disease: Benefits versus Risks

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Abstract

Background: Cardiovascular disease (CVD) remains a major global health issue. The use of statins in people with a history of CVD is generally well established, however, debate remains about their use for primary prevention in people without CVD. This narrative review aims to present studies related to the benefits and risks of taking statins for primary prevention of CVD. An internet search of the Cochrane Library (2006 to 2021) and PubMed (2006 to 2021) used the following keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors, statin OR statins; cardiovascular disease, heart disease, coronary disease; primary prevention. Systematic review/ meta-analyses-based articles were included in the review. The studies reported positive outcomes of statins, particularly in relation with reduction in all-cause mortality, non-fatal MI, and non-fatal stroke. Some adverse events were also reported, such as muscle problems, diabetes, liver dysfunctions, and renal and eye disorders, However, the risks attributable to statins were considerably lower and thus did not outweigh the benefits in preventing CVD. It should be acknowledged that the decision to initiate statins for primary prevention should not solely depend on the LDL-C value, but also on overall CVD risk factors for a particular individual, as can be seen in three major guidelines from the American College of Cardiology/ American Heart Association (ACC/AHA) - 2019, Canadian Society of Cardiology (CCS) - 2021, and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) - 2019. The risks attributable to statins were relatively low, and thus did not outweigh the benefits in preventing CVD.

Keywords: statin, primary prevention, cardiovascular risk factor, cardiovascular disease

Introduction

Cardiovascular disease (CVD) has been a global health problem due to its association with high mortality, morbidity, and total healthcare expenditure [1]. Atherosclerosis is known as the major leading

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cause of CVD, including: ischemic heart disease (IHD) or coronary artery disease (CAD), cerebrovascular disease (such as ischemic stroke), and diseases in the aorta and arteries (such as: peripheral vascular disease, PVD) [1, 2]. Global health expenditures attributable to CVD have been projected to rise as much as 22% by 2030, i.e., from 863 billion US $ in 2010 to 1,044 billion US $ in 2030 [2].

Several factors contribute to the incidence of CVD, known as cardiovascular risk factors, including hypertension, smoking, diabetes mellitus (DM), physical inactivity, unhealthy diet, dyslipidemia, overweight and obesity, age, sex, family history of premature CVD and psychosocial risk factor [3, 4]. Dyslipidemia is a general term used to explain lipid abnormalities in human body. One of lipid fractions circulating in human blood is low-density lipoprotein cholesterol (LDL-C). The relationship between a high plasma concentration of LDL-C and the development of atherosclerotic plaque has been well studied [5, 6]. Hence, the management of high LDL-C gets the most attention to control the incidence of CVD [4].

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors or statins are a group of lipid-lowering drugs with a strong effect on LDL-C lowering activity [3, 4]. There are seven statins currently available in the market, i.e., pravastatin, lovastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin. Each statin has its own potency in the LDL-C reduction effect, and based on their potency, statins can be classified as high or low potency. High potency statins, e.g., atorvastatin and rosuvastatin, decrease the LDL-C level by >50% while low potency statins, e.g., simvastatin, pravastatin, lovastatin, and fluvastatin, decrease the LDL-C level by <30% [7].

The use of statins in people with a history of CVD is generally well established, however, debate remains about their use for primary prevention in people without CVD [3, 4]. The controversy is mainly related to uncertainty about whether the benefits of statins outweigh the risks and whether widespread use of statins can be justified from a societal perspective. Hence, this narrative review aimed to present studies related to the benefits and risks of taking statins for primary prevention of CVD.

This narrative review included systematic review/meta-analyses-based publications. We searched The Cochrane Library (2006 to 2021) and PubMed (2006 to 2021) using the following keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors, statin OR statins; cardiovascular disease, heart disease, coronary disease; primary prevention. Results from searches on those databases were reviewed to identify systematic review/meta-analyses-based articles relevant to this review.

Benefits of Statins in Primary Prevention of CVD

Mortality Outcomes

All-Cause Mortality

All-cause mortality. Ray et al. [8] clearly indicated non-significant benefit of using statins for primary prevention of CVD on overall mortality. The relative risks (RRs) of overall mortality analyzed using random effect and fixed effect method were 0.91 (95% CI: 0.83-1.01) and 0.93 (95% CI: 0.86-1.00), respectively. Several meta-analyses found significant benefit of using statins for this final outcome with the RR in the range of 0.86-0.93 [9-12]. A recent meta-analysis conducted by Yebyo et al. [13] showed that statins reduced the incidence of all-cause mortality, however, significant effects were only demonstrated for pravastatin, atorvastatin, and rosuvastatin.

Although the use of statins showed significant benefits related to the overall mortality in all of the meta-analyses, the 95% confident intervals (CIs) were relatively close with the value of non-significant difference, which is 1. Furthermore, after excluding studies without reported allocation of concealment, Mills et al. [10] found non-significant benefit of using statins in terms of overall mortality, and even preferable for the non-statin users, with an RR of 1.14 (95% CI: 1.01-1.28). A study conducted by Brugts et al. [9] also found the 95% CI getting closer to 1 after excluding patients with a history of CVD events (RR 0.87; 95% CI: 0.81-0.97). The other two studies did not further analyze this effect by excluding the possible confounding factors [11, 12]. The summary findings are presented in Table 1.

Table 1. Summary of risk reduction of various final outcomes on the use of statins

Outcome	Tonelli et al. [11]				Mills et al. [10]	Ray et al. [8]	Brugts et al. [9]	Taylor et al. [12]	Yebyo et al. [13]
	Total	High Potency Statins	Low Potency Statins	High versus Low Potency Statins					
Mortality outcomes									
All-cause mortality	n = 19/78,321 RR 0.90 (0.84-0.97) NNT: 239 (149-796)	RR 0.85 (0.74-0.96)	RR 0.90 (0.79-1.03)	RR 0.94 (0.79-1.13)	n = 19 /63,899 RR 0.93 (0.87-0.99)	n = 11 /65,299 Random effect: RR 0.91 (0.83-1.01) Fixed effect: RR 0.93 (0.86-1.00)	n = 9/67,476 random effect: RR 0.88 (0.81-0.96) Fixed effect: RR 0.90 (0.84-0.96)	n = 13/48,060 RR 0.86 (0.79-0.94)	n = 24 trials RR 0.89 (0.85-0.93)
CVD death					n = 17/59,469 random effect RR 0.89 (0.81-0.98)		n = 5/34,225 random effect RR 0.88 (0.73-1.05) fixed effect RR 0.88 (0.73-1.05)		n = 15 trials RR 0.80 (0.71-0.91)
Non-CVD death					n = 18/63,333 random effect RR 0.98 (0.90.0-1.07)				
CVD event outcomes									
Any MI	n = 13/48023 RR 0.63 (0.50-0.79) NNT 216 (160-381)	6 RR 0.47 (0.31-0.71)	RR 0.68 (0.53-0.87)	RR 0.69 (0.43-1.12)	n = 17/52,976 random effect RR 0.77 (0.63-0.95)			n = 14/48,049 10 Combined fatal and non-fatal CHD events RR 0.73 (0.67-0.80)	
Fatal MI	n = 8/31424 RR 0.96 (0.50-1.85)	RR 1.54 (0.61-3.89)	RR 0.59 (0.23-1.51)						n = 6 trials RR 0.72 (0.50-1.03)
Non-fatal MI	n = 10/49222 RR 0.64 (0.49-0.84) NNT 153 (108-343)	RR 0.47 (0.34-0.67)	RR 0.77 (0.59-1.00)				n = 4/35,067 random effect RR 0.56 (0.41-0.76) fixed effect RR 0.61 (0.52-0.73)		n = 16 trials RR 0.62 (0.53-0.72)
Stroke	n = 14/60841 RR 0.83 (0.74-0.93) NNT 291 (190-707)	6 RR 0.7 (0.55-0.87)	RR 0.89 (0.77-1.03)	RR 0.79 (0.61-1.02)	n = 18/57,430 random effect RR 0.88 (0.78-1.00)		n = 9/67,476 fixed effect RR 0.82(0.74-0.91) random effect: 0.81 (0.71-0.93)	n = 10/40,295 Combined fatal and non-fatal stroke RR 0.78 (0.68-0.89)	
Fatal stroke	n = 5/36118 RR 0.91 (0.65-1.29)	RR 0.50 (013-2.00)	RR 0.95 (0.67-1.35)					n = 3/27,238 fixed effect RR 0.63 (0.18-2.23)	n = 6 trials RR 0.79 (0.53-1.19)
Non-fatal stroke	n = 9/37333 RR 0.81 (0.68-0.96) NNT 335 (199-1592)	RR 0.51 (0.33-0.79)	RR 0.88 (0.73-1.06)					n = 5/28,097 fixed effect RR 0.69 (058-0.83)	n = 16 trials RR 0.83 (0.75-0.92)
CVD events (composite)					n = 17/53,371 random effect RR 0.85 (0.77-0.95)		n = 8/47,769 random effect RR 0.70 (0.61-0.81) fixed effect RR 0.84 (0.61-0.81)	n = 9/23,805 RR 0.75 (0.70-0.81)	n = 23 RR 0.74 (0.67-0.81)

Abbreviations: RR, risk reduction; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; NNT, number needed to treat. Value of RR or NNT (95% CI). n = number of trials/ number of participants.

CVD or Non-CVD Death

Two meta-analyses analyzed the CVD mortality outcome (see Table 1). Mills et al. [10] found significant benefit of using statins for CVD mortality outcome with an RR of 0.89 (95% CI: 0.81-0.98), however the 95% CI was close to non-significant difference value.

After excluding studies with no report on allocation of concealment, the pooled analysis yielded contradictory results (RR 1.23, 95% CI: 1.02-1.49), thus favoring the group without statins [10]. The meta-analysis by Brugts et al. [9] clearly presented non-significant benefit with an RR of 0.88 (95% CI: 0.73-1.05) by using both random-effect and fixed effect analysis. Mills et al. [10] did a subgroup analysis by including studies recruiting only low-risk population. Although the result showed a significant benefit for the statin group compared with the non-statin group (RR 0.66; 95% CI :0.5-0.87), this study might suffer from some bias. The inclusion of only CVD low-risk patients means to include relatively healthier and younger subjects, thus lower CVD mortality for this group might not solely be caused by using statins [10]. Only one study analyzed the non-CVD mortality, Mills et al. [10] found non-significant benefit of using statins for non-CVD mortality with an RR of 0.98 (95% CI: 0.9-1.07). A more recent meta-analysis reported that statins were associated with a 21% RR reduction of CVD mortality (RR 0.80, 95% CI: 0.71 to 0.91; individually, only the effect of rosuvastatin and pravastatin reached statistical significance [13].

CVD Event Outcomes

CVD Events (Composite)

CVD outcomes are usually defined as combined outcomes between coronary heart disease (CHD) and stroke. Similar to CVD mortality outcome analysis, Mills et al. [10] also reported significant benefit of using statins in terms of major CVD event outcomes in the beginning of their analysis with a RR for the statins group of 0.85 (95% CI: 0.77-0.95). But after excluding studies with no report of allocation of concealment, they found preferable results for the group without statins (RR 1.09; 95% CI: 1.01-1.20) [10]. A meta-analysis conducted by Taylor et al. [12] divided CVD outcomes into total CVD events, fatal CVD events, and non-fatal CVD events (RR 0.75, 95% CI: 0.70-0.81; RR 0.83, 95% CI: 0.72-0.96; and RR 0.77, 95% CI: 0.62-0.96, respectively). While Yebyo et al. [13] reported significant composite major cardiovascular events (excluding fatal stroke and heart failure) on the use of statins (RR 0.74, 95% CI: 0.67–0.81). Since CVD outcomes are composite outcomes, it is interesting to analyze the results for CHD outcomes and stroke outcomes separately.

Myocardial Infarction (MI)

Four studies observed MI outcomes reported some benefits of using statins in term of CHD or MI outcomes (Table 1). Tonelli et al. [11] showed non-significant benefit of statins for fatal MI with a RR of 0.96 (95% CI: 0.5-1.85) but significant benefit for non-fatal MI with a RR of 0.64 (95% CI: 0.49-0.84). Brugts et al. [9] and Yebyo et al. [13] also found significant benefit of statin s only in non-fatal MI (RR 0.56, 95% CI: 0.41-0.76 [random effect analysis] and RR 0.61, 95%CI: 0.52-0.73 [fixed effect analysis]; and RR 0.62, 95% CI: 0.53 to 0.72, respectively). By excluding studies without allocation of concealment, Mills et al. [10] found non-significant benefit of using statins for MI outcome (RR 1.16; 95% CI: 1.01-1.35). Unfortunately, this study did not differentiate the analysis based on fatal and non-fatal MI. Differentiation of MI might be helpful to identify in which condition statins should be given. Non-fatal MI might be the only outcome for which most studies reported significant benefits.

Stroke

The analysis of five studies showed stroke outcomes (Table 1). Without differentiating the type and severity of stroke, the studies conducted by Mills et al. [10] and Brugts et al. [9] presented contrary results. Even after excluding studies without allocation concealment, Mills et al. [10] found non-significant benefit of using statins in term of stroke outcome with an RR of 0.88 (95% CI: 0.78-1.00)]. On the other hand, Brugts et al. [9] found significant benefit of statins with an RR of 0.81 (95% CI: 0.71-0.93) with random effect or 0.82 (95% CI: 0.74-0.91) with fixed effect analysis. This might be due to the different proportion of patients with hemorrhagic stroke in studies included in each meta-analysis in which the use of statins might be less beneficial.

Moreover, there was a difference in the proportion of patients with particular severity of stroke included in each meta-analysis. The other two meta-analyses emphasized the importance to differentiate the level of stroke severity [11, 12]. Both studies found non-significant benefit of statins for fatal stroke with an RR of 0.91 (95% CI: 0.65-1.29) and 0.63 (95% CI: 0.18-2.23), while a significant benefit of statins for non-fatal stroke was reported. The recent meta-analysis by Yebyo et al. [13] confirmed this finding (fatal stroke: RR 0.89, 95% CI: 0.85–0.93; non-fatal stroke: RR 0.83, 95% CI: 0.75–0.92).

The Relationship between LDL Reduction and Outcomes in Primary Prevention of CVD

There were two meta-analyses that examined the relationship between LDL reduction and outcomes in primary prevention. Presented as beta (β) coefficient, Mills et al. [10] reported no relationship between LDL reduction and overall mortality and CVD mortality outcomes (β coefficient -0.07; 95% CI: -0.22 to 0.06, p = 0.29 and 0.11; 95% CI: -0.11 to 0.34, p = 0.33, respectively). This is in line with the findings from Ray et al. [8] where no significant relationship between LDL-C reduction with overall mortality outcomes was reported, either measured as an absolute reduction (p = 0.62) or percentage reduction in LDL-C (p = 0.46). These findings, together with the findings on the effectiveness of statins on the various outcomes, have strongly indicated no further benefits in tightly and rashly controlling LDL-C in primary prevention setting.

Risks of Taking Statins as Primary Prevention of CVD

Statins have been reported to be associated with some adverse effects, such as cancer, muscle problems, diabetes, changes in liver function tests (aminotransferases), and renal and eye disorders (Table 2).

Cancer

Studies on the effects of statin use and cancer events are presented in Table 2. Most of those studies showed no significant effect of statin therapy on the incidence of cancer or mortality thereof in any site. Just one meta-analysis of case-control studies from Taylor et al. [14] found a significant association between statin usage and cancer, prominently in colon cancer (odds ratio [OR] 0.89; 95% CI: 0.82-0.97). The questionable finding on the significant association between statin and colon cancer should be addressed since most studies were conducted in Western countries, where colon cancer was common due to habitual diets. On the other hand, recent studies have increasingly explored anticancer properties of statins due to their antiproliferative effects [15].

Diabetes Mellitus

Four meta-analyses investigated the association between DM and statins use (Table 2). Alberton et al. [21] analyzed the risk of DM from every single statin separately. There was no association found between simvastatin and risk of DM [21]. Two meta-analyses reported an effect of statins as a group and the risk of DM [22, 23]. Both studies found statin prescription increased the risk of DM. Unfortunately, the studies included in each meta-analysis did not account for several DM risk factors, especially familial history of DM, into the findings. Cooney et al. [24] tried to differentiate the association of intensive versus moderate dose of statins and the risk of DM. Intensive doses of statins reportedly increased the risk of new-onset DM compared to moderate doses of statins. Interestingly, 75% of DM diagnoses were based on a non-biochemical methods, i.e., initiation of glucose lowering treatment within the study period. Unfortunately, the studies did not consider how many participants were already in DM treatment at the start of recruitment. A recent meta-analysis reported no association on the use of statins for primary prevention with the incidence of diabetes [25].

Muscle Disorders

A recent meta-analysis classified muscle problems as self-reported symptoms or clinically confirmed disorders, to resolve the inconsistency and variety of definitions of outcomes in the trials included. The results showed that statins are associated with a small increased risk of muscle symptoms, but no adequate evidence for muscle disorders [25]. Most of the previous reviews also reported no associations between statins and rhabdomyolysis (Table 2).

Table 2. Summary of adverse drug events related to the use of statins

Studies	Results
Cancer	
Mills et al. [10]	RR of cancer compared with placebo: 1.02 (95% CI 0.94-1.11)
Brugts et al. [9]	RR of cancer compared with placebo: 0.97 (95% CI 0.89-1.05)
Ray et al. [8]	RR of cancer compared with placebo 1.00 (95% CI 0.93-1.08)
Matushita et al. [16]	Pravastatin 10-20 mg vs diet Effect of pravastatin on: • Cancer incidence HR, 0.99 (95% CI 0.81–1.19) • Cancer mortality HR, 0.86 (95% CI 0.61–1.21)
Taylor et al. [14]	OR, 95% CI • Any cancer 0.71 (0.56-0.89) • Breast cancer 0.86 (0.60-1.23) • Colon cancer 0.89 (0.82-0.97) • Lung cancer 0.75 (0.50-1.11) • Prostate cancer 0.74 (0.45-1.20)
Baigen et al. [17]	• Intensive vs less statins in any site of cancer: RR 1.02 (95% CI 0.89-1.18) • Statins vs control in any site: RR 1.00 (95% CI 0.95-1.04) • All trials combined: RR 1.00 (095% CI .96-1.04)
Bonovas et al. [18]	• Pooled data: RR 0.99 (095% CI .94 to 1.04); n = 35 trials • Major RCT, follow up >5.3 years: RR 1.01 (95% CI 0.96 to 1.06); n = 9 trials
Browning et al. [19]	n = 26 trials Any cancer: pooled RR 1.00 (95% CI 0.95–1.05; I^2 = 0%) • Breast cancer (7 trials): RR 1.01 (95% CI 0.79–1.30; I^2 = 43%) • Prostate cancer (4 trials): RR 1.00 (95% CI 0.85–1.17; I^2 = 0%) • Colorectum cancer (9 trials): RR 1.02 (0.89–1.16; I^2 = 0%) • Lung cancer (9 trials): RR 0.96 (95% CI 0.84–1.09; I^2 = 0%) • Genito-urinary cancer (5 trials): RR 0.95 (95%CI 0.83–1.09; I^2 = 0%) • Melanoma cancer (4 trials): RR 0.86 (95% CI 0.62–1.20; I^2 = 17%) • Gastric cancer (1 trial): RR 1.00 (95% CI 0.35–2.85)
Emberson et al. [20]	Effect of statin therapy on: Cancer incidence RR (95% CI) per 1 mmol/Lin LDL-C • Statins vs control: RR 1.00 (0.96-1.04) • Intensive statins vs less: RR 1.02 (0.89-1.18) • All: RR 1.00 (0.96-1.04) Cancer mortality RR (95%CI) per 1 mmol/Lin LDL-C • Statin vs control: RR 1.00 (0.93-1.07) • Intensive statins vs less: RR 0.88 (0.67-1.15) • All: RR 0.99 (0.92-1.06)
Alberton et al. [21]	Atorvastatin vs control (n = 6/11,763): OR: 0.90 (95% CI 0.74-1.11) Simvastatin vs control (n = 4/25,443): OR 1.00 (95% CI 0.91-1.10)
Diabetes mellitus	
Alberton et al. [21]	Atorvastatin vs control: NO DATA Simvastatin vs control (n = 2/24,980): OR 1.10 (95% CI 0.97-1.25)
Cooney et al. [24]	New-onset diabetes (n = 5/35,752): intensive treatment vs moderate: OR 1.12 (95% CI 1.04-1.22; I^2 = 0%)
Rajpatak et al. [22]	Statin vs control (n = 6/57,593): RR 1.13 (95% CI 1.03–1.23)
Sattar et al. [23]	Statin vs control (n = 13/57,593): OR 1.09 (5% CI 1.02-1.17)
Cai et al. [25]	Statin vs control (n = 9 trials): OR 1.01 (95% CI 0.88 to 1.16)
Muscle problems	
Mills et al. [10]	(n = 10/45,469) RR-random effect: 1.02 (95% CI 0.94-1.11) for rhabdomyolysis
Ray et al. [8]	(n = 6/52,027) RR-random effect: 0.97 (95% CI 0.89-1.05) for rhabdomyolysis RR-fixed effect: 0.97 (95% CI 0.89-1.05) for rhabdomyolysis
Tonelli et al. [11]	(n = 4/31,818) RR-random effect: 1.00 (95% CI 0.93-1.08) for rhabdomyolysis
Taylor et al. [12]	(n = 11/38,739) RR-random effect: 1.01 (95% CI 0.93-1.10) for rhabdomyolysis
Cai et al. [25]	Statins vs control (n = 21 trials): OR 1.06 (95% CI 0.01 to 1.13); RD 15 (95% CI 1 to 29) for self-reported muscle symptoms Statins vs control (n = 25 trials): OR 0.88 (95% CI 0.62 to 1.24); RD 0 (95% CI -1 to 1) for muscle disorders
Liver dysfunction	
Alberton et al. [21]	Simvastatin vs control (n = 2/24,980) Increase AST: NO DATA Increase ALT: OR 1.42 (95% CI 1.03–1.96) Atorvastatin vs Pravastatin control (n = 6): Increase AST: OR 2.27 (95% CI 1.19–4.30) Increase ALT: OR 1.74 (95% CI 0.50–6.07)
Josan et al. [26]	More vs less intensive therapy: OR 4.14 (95% CI 2.30–7.44) Less intensive vs placebo: OR 1.23 (95% CI 1.06–1.42) 95% CI
Cai et al. [25]	Statins vs control (21 trials): OR 1.33 (95% CI 1.12 to 1.58); RD 8 (95% CI 3 to 14)
Renal insufficiency	
Cai et al. [25]	Statins vs control (n = 8 trials): OR 1.14 (95% CI 1.01 to 1.28); RD 12 (95% CI 1 to 24)
Eye problems	
Cai et al. [25]	Statins vs control (n = 6 trials): OR 1.23 (95% CI 1.04 to 1.47); RD 14 (95% CI 2 to 29)

Abbreviation: OR, odds ratio; RD, risk difference; CI, confidence interval; AST, aspartate transferase; ALT, alanine transferase.

Table 3. Summary of guideline recommendations for primary prevention with statins

Guidelines	Recommended indications for primary prevention with statins
2019 ACC/AHA [3]	• Patients ages 20-75 years and LDL-C ≥190 mg/dl, use high-intensity statins without risk assessment. • T2DM and age 40-75 years, use moderate-intensity statins and risk estimate to consider high-intensity statins. • Age >75 years, clinical assessment and risk discussion. • Age 40-75 years and LDL-C ≥70 mg/dl and <190 mg/dl without diabetes, use the risk estimator that best fits the patient and risk-enhancing factors to decide intensity of statins.
2019 ESC/EAS [28] (Class 1/A recommendations)	• Lipid-based: – LDL-C ≥4.9 mmol/L (190 mg/dL) or – TC >8 mmol/L (309 mg/dL) • Risk-based: – Age 40–75 years, LDL-C ≥2.6 mmol/L (100 mg/dL), SCORE 5% to <10% or – Age 40–75 years, LDL-C ≥1.8 mmol/L (70 mg/dL), SCORE ≥10% or – Diabetes or Non-dialysis dependent CKD and eGFR <60 mL/min/1.73 m2
2021 CCS [29]	• Those with an LDL-C of ≥5 mmol/L and those with a statin indicated condition such as diabetes mellitus or chronic kidney disease (except those receiving dialysis) regardless of estimated FRS risk. • Individuals with an estimated 10-year FRS risk of ≥20% (high risk), and those 10-19.9% (intermediate FRS risk) who have LDL-C greater than 3.5 mmol/L (135 mg/dL), non-HDL-C >4.2 mmol/L (162 mg/dL), or ApoB >1.05 g/dL. Men ≥50 and women ≥60 with other risk factors such as hypertension, impaired glucose tolerance, smoking, central adiposity, or other risk modifiers such as hsCRP ≥ 2.0mg/L, non-zero coronary artery calcification, Lp(a) ≥50 mg/dL (100 nmol/L) or family history of premature CHD are also classified as intermediate risk for whom a statin is recommended.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association AHA; CCS, Canadian Society of Cardiology; FRS, Framingham Risk Score; CHD, coronary heart disease; CKD, chronic kidney disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FRS, Framingham Risk Factor; LDL-C, low-density lipoprotein cholesterol; HDL, high-density cholesterol; TC, total cholesterol; T2DM, Type-2 Diabetes Mellitus.

Aminotransferase Levels

Statins increased the risk of elevated liver enzymes, either aspartate transaminase (AST) or ALT (alanine transaminase) (Table 2). The use of atorvastatin was significantly associated with elevated AST and the use of simvastatin was significantly associated with elevated ALT [21]. The more intensive the dose, the larger increase in risk of elevated liver enzymes [26]. A recent meta-analysis confirmed the association of taking statins with liver dysfunction (OR 1.33, 95% CI: 1.12 to 1.58; absolute risk difference [RD] 8, 95% CI: 3 to 14) [25].

Renal Insufficiency and Eye Problems

A meta-analysis by Cai et al. [25] confirmed associations between statins and renal insufficiency and eye problems (Table 2). However, the diagnoses and measurements of these two outcomes in the included trials in this review varied, thus the associations might be limited to non-specific renal disorders and cataracts.

Further, Cai et al. [25] (n = 58 trials) constructed network meta-analyses on the associations of individual statins with adverse effects. Rosuvastatin was associated with an increased risk of self-reported muscle symptoms (OR 1.09; 95% CI: 1.01 to 1.16), renal insufficiency (OR 1.13; 95% CI: 1.00 to 1.28), diabetes (OR 1.14; 95% CI: 1.00 to 1.30), and eye conditions (OR 1.26; 95% CI: 1.04 to 1.52). Atorvastatin (OR 11.41; 95% CI: 1.08 to 1.85) and lovastatin (OR 1.81; 95% CI: 1.23 to 2.66) increased the risk of liver dysfunction. For comparison among different statins, a higher risk of liver dysfunction was reported for fluvastatin and pravastatin compared to fluvastatin and pravastatin; while atorvastatin and rosuvastatin had a higher risk of diabetes than pitavastatin [20]. Overall, the risks attributable to statins were low, thus did not outweigh the benefits in preventing CVD.

Guideline Recommendations on the Use of Statins for Primary Prevention of CVD

While continuous research has proven statins' potential benefits, many major guidelines have included statins for primary prevention of CVD [27]. Table 3 presents summary recommendations from three major guidelines, i.e., guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), Canadian Society of

Cardiology (CCS), and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS). The AHA statistics update in 2022 reported the increasing use of statins among US adults with a 10-year predicted ASCVD risk ≥7.5% from 27.9% (between 2005 to 2006) to 32.5% (between 2015 to 2016) [30].

Limitations

While this narrative review could provide a broader perspective on the use of statins for primary prevention; as for all narrative reviews, selection bias cannot be excluded.

Conclusion

The risks attributable to statins were relatively low; thus, they did not outweigh the benefits in preventing CVD. However, the decision to initiate statins for primary prevention should not solely depend on the LDL-C value, but also on overall CVD risk factors for a particular individual.

Ethical Compliance

The authors declare that they have no conflicts of interest with this work and that they did not receive any funding for this work. If this work involved human participants, informed consent was received from each individual, and the work was conducted in accordance with the 1964 Declaration of Helsinki. If this work involved experiments with humans or animals, it was conducted in accordance with the related institution's research ethics guidelines.

References

[1] Mendis S. Global progress in prevention of cardiovascular disease. *Cardiovasc Diagn Ther* 2017; 7 (Suppl 1): S32-S38. doi: 10.21037/cdt.22017.21003.21006.

[2] Bloom D, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom L, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, Pretner K, Rosenberg L, Seligman B, Stein AZ, Weinstein C. The Global Economic Burden of *Noncommunicable Diseases*. *Geneva: World* Economic Forum; 2017. 46 pp.

[3] Arnett D, Blumenthal R, Albert M, Buroker A, Goldberger Z, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 140: e596-e646.

[4] ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42: 3227-3337.

[5] Boekholdt S, Arsenault B, Mora S, Pedersen T, LaRosa J, Nestel P, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM Jr, Ridker PM, Kastelein JP. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012; 307 (12): 1302-1309. doi: 10.1001/jama.2012.366.

[6] Mortensen M, Nordestgaard B. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. *Lancet* 2020; 396 (10293): 1644-1652. https://doi.org/1610.1016/S0140-6736(1620)32233-32239.

[7] Chou R, Dana T, Daeges M, Jeanne T. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2016; 316 (19): 2008-2024. doi: 2010.1001/jama.2015.15629.

[8] Ray K, Seshasai S, Erqou S, Sever P, Jukema W, Ford I, Sattar N. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med* 2010; 170 (12): 1024-10231.

[9] Brugts J, Yetgin T, Hoeks S, Gotto A., Sheperd J, Westendorp R., de Craen AJ, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009; 338: b.2376. doi: 2310.1136/bmj.b2376.

[10] Mills E, Rachlis B, Wu P, Devereaux P, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 2008; 52 (22): 1769-1781.

[11] Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, Klarenbach S, McAlister FA, Wiebe N, Manns B; Alberta Kidney Disease Network. Efficacy of

statins for primary prevention in people at low cardiovascular risk: a meta-analysis. *Can Med Assoc J* 2011; 183 (16): e1189-1197. doi: 10.1503/cmaj.101280.

[12] Taylor F, Huffman M, Macedo A, Moore T, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2013; Issue 1: Art. No.: CD004816. doi:10.1002/14651858.CD004816.pub5.8:b2376.

[13] Yebyo H, Aschmann H, Kaufmann M, Puhan M. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *Am Heart J* 2019; 210: 18-28.

[14] Taylor M, Wells B, Smolak M. Statins and cancer: a meta-analysis of case-control studies. *Eur J Cancer Prev* 2008; 17: 259-268.

[15] Barbalata C, Tefas L, Achim M, Tomuta I, Porfire A. Statins in risk-reduction and treatment of cancer. *World J Clin Oncol* 2020; 11 (8): 573-588. doi: 510.5306/wjco.v5311.i5308.5573.

[16] Matsushita Y, Sugihara M, Kaburagi J, Ozawa M, Iwashita M, Yoshida S, Saito H, Hattori Y. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. *Pharmacoepidemiol Drug Safety* 2010; 19: 196-202.

[17] Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376, 1670-1681.

[18] Bonovas S, Filioussi K, Tsavaris N, Sitaras N. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006; 24: 4808-4817.

[19] Browning D, Martin R. Statins and risk of cancer: a systematic review and metaanalysis. *Int J Cancer* 2007: 120*:* 833-843.

[20] Cholesterol Treatment Trialists' (CTT) Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One* 2012; 7: e29849.

[21] Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. *QJM* 2012; 105: 145-157.

[22] Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diab Care* 2009; 32: 1924-1929.

[23] Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735-742.

[24] Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk a review for clinicians. *J Am Coll Cardiol* 2009; 54 (14): 1209-1227.

[25] Cai T, Abel L, Langford O, Monaghan G, Aronson J, Stevens R, Lay-Flurrie S, Koshiaris C, McManus RJ, Richard Hobbs FD, Sheppard J. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* 2021; 374: n1537. doi: 1510.1136/bmj.n1537.

[26] Josan K, Majumdar S, Mcalister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *Can Med Assoc J* 2008; 178, 576-584.

[27] Singh RB, Fedacko J, Elkilany GN, Palmiero P, Hristova K, Cornelissen G. Statins administration for primary prevention of stroke and coronary artery disease: A scientific statementof the International College of Cardiology. *World Heart J* 2019; 11(4): 255-260.

[28] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111-188.

[29] Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Piché ME, Poirier P, Sievenpiper J, Stone J, Ward R, Wray W. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol* 2021; 37: 1129-1150.

[30] Tsao CW, Aday AW, Almarzooq FI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Ferguson JF, Generoso G, Ho JE, Kalani R, Khan SS, Kissela BM, Knutson KL, Levine DA, Lewis TT, Liu J, Loop MS, Ma J, Mussolino ME, Navaneethan SD, Perak AM, Poudel R, Rezk-Hanna M, Roth GA, Schroeder EB, Shah SH, Thacker EL, VanWagner LB, Virani SS, Voecks JH, Wang NY, Yaffe K, Martin SS. Heart disease and stroke statistics -- 2022 update: A report from the American Heart Association. *Circulation* 2022; 145 (8): e153-639. https://doi.org/10.1161/CIR.0000000000001052.

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