Journal of Medical Sciences and Health Care Research ISSN: 3068-9104

PRIME OPEN ACCESS

Volume 2, Issue 2

Systematic Review

Date of Submission: 11 Sep, 2025
Date of Acceptance: 15 Oct, 2025
Date of Publication: 21 Oct, 2025

Importance of Absolute Low-Density Lipoprotein Cholesterol Reduction: A Systematic Review of 58,778 Participants from 10 Randomized Trials

Bishnu Mohan Singh[1], Hari K. Lamichhane[2], Narayan Bohara[3], Faiza Ahmed[4*], Faiza Zakaria[5], Prabhat Adhikari[6], Sistu K.C[1], Binod K.C.[7], Puja Singh[8], Tripti Sharma[9], Zouina Sarfraz[10], Jeevan Gautam[11], Uzoamaka Nwokorie[12], Endrit Shahini[13], Sai Harsha Bobba[14], Antonino La Spada[15], Akshay Patel[16], Sravya Gudapati[17], Godsgift Enebong Nya[18] and Yasar Sattar[19]

[1]Department of Emergency and General Medicine, Patan Academy of Health Sciences, Lalitpur, Nepal
[2]Department of Internal Medicine, New York Medical College (Metropolitan) Program, New York, United States of America
[3]Oxford University Clinical Research Unit, Patan Academy of Health Sciences, Lalitpur, Nepal
[4]Division of Clinical and Translational Research, Larkin Community Hospital, United States of America
[5]Department of Internal Medicine, Dow Medical College, Karachi City , Sindh, Pakistan
[6]Department of Infectious Diseases and Critical Care, Grande International Hospital, Kathmandu, Nepal
[7]Department of Internal Medicine, Upstate University Hospital, New York, United States of America
[8]Department of Internal Medicine, National Medical College, Birgunj, Nepal
[9]Department of Internal Medicine, Lumbini Medical College, Lumbini, Nepal
[10]Department of Internal Medicine, Fatima Jinnah Medical University, Lahore, Pakistan
[11]Department of Internal Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal
[12]Department of Medicine, University of Science, Arts and Technology, Olveston, Montserrat, British West Indies
[13]Division of Gastroenterology, National Institute of Gastroenterology "S. De Bellis," Castellana Grotte (Bari), Italy
[14]Department of Internal Medicine, Greensboro Medical Associates, Greensboro, North Carolina, United States of America
[15]Department of Cardiology, Anthea Hospital GVM care and research, Bari, Italy
[16]Department of Cardiology, Mac Neal Hospital, Berwyn, Illinois, United States of America
[17]Department of Cardiology, Premier Heart and Vascular Center, Florida, United States of America
[18]Department of Cardiology, John Hopkins Hospital, Baltimore, Maryland, United States of America
[19]Department of Cardiology, West Virginia University - J.W. Ruby Memorial Hospital, Morgantown, West Virginia, United States of America

Author contributions: All authors contributed to the conception, writing, and review of the article and approved the submitted version.

***Corresponding Author:**
Faiza Ahmed, Division of Clinical and Translational Research, Larkin Community Hospital, South Miami, FL 33143, United State if America

Citation: Singh, B. M., Lamichhane, H. K., Bohara, N., Ahmed, F., Zakaria, F., et.al. (2025). Importance of Absolute Low-Density Lipoprotein Cholesterol Reduction: A Systematic Review of 58,778 Participants from 10 Randomized Trials. *J Med Sci Health Care Res, 2*(2), 01-21.

Abstract

Background: Statins are drugs that lower the level of low-density lipoprotein cholesterol (LDL-C). Statins lower LDL-C in both populations with high and low mean baseline LDL-C concentrations, preventing cardiovascular disease (CVD) and mortality. Hence, it is essential to study the relationship between the amount of decrease in LDL-C level with statins and the prevention of CVD. The central objective of this systematic review is to determine the relationship between the amount of LDL-C reduction with statins and primary prevention of CVD or mortality.

Methods: We identified published articles in electronic databases, including Google Scholar, PubMed, Cochrane Library, and PubMed Central. Two reviewers independently screened the articles via Covidence software, and an assessment of the quality of included studies was done via the Cochrane risk of bias assessment tool. We analyzed the primary endpoint of selected Randomized Clinical Trials (RCTs) in terms of hazard ratio (H.R.) or risk ratio (R.R.). We associated the primary endpoint with the amount of LDL-C reduction achieved in the RCTs. For those RCTs whose primary endpoint was non-clinical, we analyzed the secondary endpoint or other clinical outcomes.

Results: Based on our eligibility criteria, we included ten RCTs in our review. Statistically significant clinical outcomes were associated with the reduction of LDL-C in seven RCTs. In the remaining three RCTs, a significant reduction in LDL-C was achieved, but the clinical outcome was statistically insignificant.

Conclusion: Our systematic review proves an association of the amount of LDL-C reduction with primary prevention of CVD and mortality. Further research is warranted to quantify these associations. Based on current evidence, the amount of LDL-C reduction seems more predictable for reducing cardiovascular events (CVEs) or mortality among populations. Therefore, clinical guidelines on statins should focus on the amount of LDL-C reduction for primary prevention of CVD and mortality rather than baseline LDL-C.

Keywords: Cardiovascular Diseases, Mortality, LDL-Cholesterol, Lipid Lowering, Humans, Statin, Hydroxy Methyl Glut Aryl-CoA Reductase Inhibitors, Cardiovascular Events

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are the most commonly used lipid-lowering drugs. They are prominent drugs for treating hypercholesterolemia that works by inhibiting 3-hydroxy-3-methylglutaryl- coenzyme A reductase (HMGR), and blocking the conversion of HMG-CoA reductase, which is the rate-limiting enzyme required for cholesterol biosynthesis, to mevalonic acid [1]. As a result, they reduce low-density lipoprotein cholesterol (LDL-C) concentration by decreasing its synthesis in the liver and increasing removal from the peripheral circulation. They also increase high-density lipoprotein (HDL) cholesterol and reduce triglyceride concentrations [2].

Several systematic reviews and meta-analyses have assessed the primary preventive role of statins in cardiovascular disease (CVD). However, a majority of these studies also analyzed randomized controlled trials (RCTs) where at least 80% of participants had no prior CVD [3,4]. Additionally, some reviews examined RCTs where subjects had no prior coronary heart disease (CHD) although they were affected by other vascular diseases [5].

Moreover, some primary preventive studies conducted in developed countries' populations had average total cholesterol (T.C.) and LDL-C levels greater than 240 mg/dl and 160 mg/dl, respectively [6-8]. These studies supported statins' usefulness in reducing the chance of CVD since the developed nation populations have relatively high mean serum cholesterol concentration, and there is a direct and robust association of serum cholesterol concentration of these populations with coronary heart disease (CHD) [6-15]. Therefore, lowering cholesterol levels in developed nation populations would have potentially reduced the occurrence of CVD.

The prospective observational study revealed that no threshold value exists above which the risk of CHD increases or below which the risk of CHD decreases [12]. The risk of CHD is extended over the whole range of the cholesterol concentration [12,13]. A study conducted in Shanghai, China, revealed that cholesterol contributed to a substantial risk of CHD in the study sample where there was normal or even below a recommended concentration of mean baseline serum cholesterol level, as per the current Western guidelines [16]. A meta-analysis which was performed by Singh et al. included clinical trials in which over 90% of individuals had been free of CVD, and the mean LDL-C concentration of included trial populations was found to be within the range of 100 to 159 mg/dl [17]. This study demonstrated that statins were effective in the primary prevention of atherosclerotic CVD, and revascularization procedures within the populations whose mean LDL-C was in the near-optimal to the borderline high range [17].

Hence, statins proved to be preventative for CVD in populations whose mean LDL-C was higher to the lower range and devoid of prior CVD. Therefore, in this scenario, it is necessary to present evidence to the scientific community addressing whether the initial LDL-C level or amount of LDL-C reduction is more predictable for the primary prevention of CVD and mortality with statins.

The primary purpose of this systematic review is to determine the relationship of the amount of LDL-C reduction by statins with primary prevention of CVD and mortality. In addition, our study also aims to analyze the role of LDL-C in current primary preventive guidelines of statin to prevent atherosclerotic cardiovascular disease (ASCVD) and correlate the findings of our research with these guidelines.

Methods

We carried out this systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) [18].

Study Protocol

We prepared the study protocol following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 (PRISMA-P 2015). We searched for articles in the electronic database according to our search strategy and registered the protocol in the Research Registry on June 17, 2021. The registered code of our protocol is reviewregistry1170.

Search Process

We searched different electronic databases, including Cochrane Library, PubMed, Google Scholar, and PubMed Central. In addition, we adjusted the search strategy to include any clinical trials, review articles, or meta-analyses of statins describing their role to prevent cardiovascular disease (CVD) and mortality in those without previous CVD from January 1, 1994, to July 2020. The search strategy used in the systematic review is shown in Supplementary Materials.

Selecting Studies

We imported the resulting articles from our search strategy into the Mendeley software, removed the duplicates, and then imported them into the Covidence software. Two authors (H.K.L. and B.M.S.) initially screened the titles and abstracts followed by the full-text, using the Covidence software. All disagreements were sorted out by discussion with other authors. The inclusion criteria of our review were as follows: (i) Randomized Clinical Trials (RCTs) of statins demonstrating its role to prevent cardiovascular disease and mortality in those without previous CVD (ii) greater than 90% participants of RCT free of prior Cardiovascular Disease (CVD) (iii) RCT follow-up of at least one year and a minimum of 100 participants in the statin group (iv) RCTs with one or more clinical outcomes in terms of cardiovascular events or mortality. The exclusion criteria of our review were as follows: (i) Non-RCT studies (ii) Studies not reporting clinical outcomes in terms of cardiovascular events or mortality (iii) Studies done on a specific group of participants like renal transplant, late chronic kidney disease (CKD), preexisting atherosclerosis, aortic stenosis, hemodialysis, human immunodeficiency virus (HIV), diabetes with glycated hemoglobin (HbA1c) ≥ 12%, familial hyperlipidemia, patients with a 10-year risk of a major coronary event or stroke ≥ 20%.

Extracting Data

From the included studies, we extracted the following information: (i) mean baseline total cholesterol (ii) mean baseline LDL-C of participants (iii) number of participants in the intervention and control group (iv) follow-up duration in years (v) percentage of participants with prior CVD (vi) mean age of participants included in the trial (vii) primary endpoint (viii) secondary endpoint (ix) other clinical outcomes (x) changes in LDL-C levels. Five authors (N.B., S.K., B.K., Z.S., and P.S.) independently extracted the information, and other authors sorted out any conflicts after detailed discussions.

Quality Assessment

We assessed the risk of bias of included RCTs using the Cochrane risk of bias 2 (ROB 2) tool. 19 On the basis of our risk of bias assessment of RCTs, we labeled the RCTs as "Low Risk," "Unclear Risk," and "High Risk." Four authors (F.A., B.M.S., J.G., and T.S.) independently evaluated the risk of bias of the included studies. Any discrepancies were sorted out with the help of additional authors.

We presented the extracted data in tabular form. In addition, we showed the demographic characteristics of participants of included clinical trials and study endpoints in two different tables. We analyzed the primary endpoint of the RCTs included in our systematic review in terms of hazard ratio (H.R.) or risk ratio (R.R.). We considered the study statistically significant if the p-value of H.R. or R.R. for the clinical outcome was <0.05 and H.R. or R.R. did not cross 1. For those RCTs whose primary endpoint was non-clinical, we analyzed the secondary endpoint or other clinical outcomes. Then we associated the primary endpoint with absolute LDL-C reduction achieved in the RCTs. We associated secondary endpoint or other clinical outcomes with absolute LDL-C reduction achieved during the study for RCTs whose primary endpoint was non-clinical.

Results

Our search strategies identified 16,572 articles (PubMed 4,911; PMC 5,362; Cochrane Library 5,002; Google Scholar 1,297). We removed 685 duplicate articles and conducted title and abstract screening of 15,887 articles. Next, we excluded 14,974 articles, and finally, 913 articles had undergone full-text screening. The proportionate agreement as per the Covidence software of two reviewers for the title and abstract screening was 0.95, while the value for full-text articles screening was 0.99. Thus, we identified ten primary preventive RCTs evaluating statins where most participants were free of CVD.6,20–28 Figure 1 illustrates the flowchart of the study selection process.

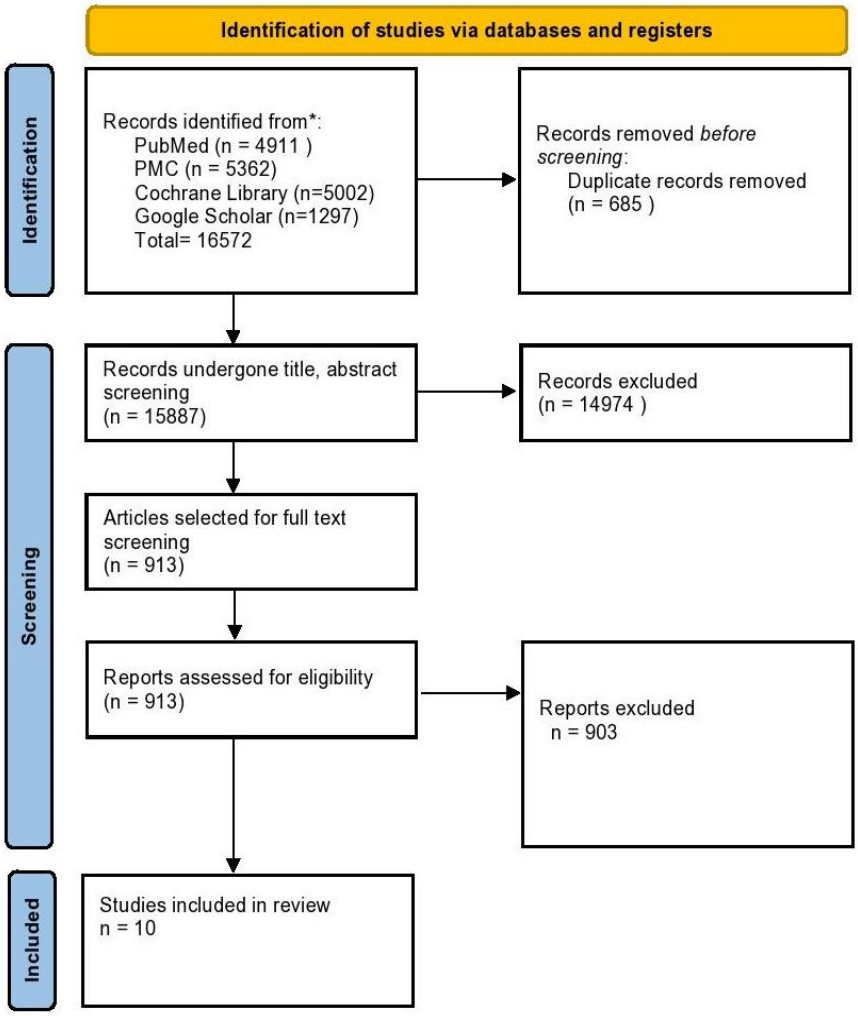

Figure 1: PRISMA Flow Diagram of the Study Selection Process Showing Articles Screening and final RCTs Selection

Table 1 describes the different clinical trials included in this review and the baseline mean serum concentration of total cholesterol and LDL-C. The included trials were WOSCOPS (West Of Scotland Coronary Prevention Study), TRACE RA (Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis), HOPE-3 (Heart Outcomes Prevention Evaluation),JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese), CARDS (Collaborative Atorvastatin Diabetes Study), Beishuizen et al., HYRIM (Hypertension High-Risk Management trial), PREVEND IT (Prevention of Renal and Vascular Endstage Disease Intervention Trial), and AFCAPS/TexCAPS (Air Force/ Texas Coronary Atherosclerosis Prevention Study) [6,20-28].

	TRACE RA 2019		*HOPE-3 2016*		*JUPITER 2008*		*MEGA 2006*		*CARDS 2004*		*Beishuizen et al., 2004*	
	Atorvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Diet plus pravastatin	Diet	Atorvastatin	Placebo	Statin	Placebo
Intervention	40 mg	na	10 mg	na	20 mg	na	10 mg uptitrated to 20 mg if T.C. did not decrease to ≤ 5.69 mmol/L	na	10 mg	na	Cerivastatin 0.4 mg; later was withdrawn from market in Aug. 2001, then then replaced with Simvastatin 20 mg	na
Country/region	United Kingdom (UK)		21 countries (Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, UK, Ukraine)		26 countries (Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, UK, Uruguay, United States, Venezuela)		Japan		UK, Ireland		Netherlands	
Study design	randomized, double-blind, placebo-controlled trial		multicenter, double-blind, randomized, placebo-controlled trial		randomized, double-blind, placebo-controlled, multicenter trial		prospective, open-labelled, blinded, randomized, controlled trial		multicentre, randomized, placebo-controlled trial		randomized, placebo-controlled, double-blind clinical trial	
n.	1,504	1,498	6361	6344	8901	8901	3866	3966	1428	1410	125	125
sex- no. (%)												
male	397	378	3410	3412	5475	5526	1228	1248	972	957	61 (49)	57 (46)
female	1,107 (74)	1,120 (75)	2951 (46.4)	2923 (46.1)	3426 (38.5)	3375 (37.9)	2638 (68)	2718 (69)	456 (32)	453 (32)	64	68
Age - years (n)	61.1 ± 8.3 (1,500)	60.9 (8.5) (1491)	65.8±6.4	65.7±6.3	yr (IQR) = 66 (60.0–71.0)	yr (IQR) = 66 (60.0–71.0)	58.2	58.4	61.5	61.8	58.8± 11.3	58.2 ± 11.4
Race or ethnic group — no. (%)												
Hispanic	na	na	1744 (27.4)	1752 (27.6)	1121 (12.6)	1140 (12.8)	na	na	na	na	na	na
White	1,394 (98)	1,407 (98)	1286 (20.2)	1260 (19.9)	6358 (71.4)	6325 (71.1)	na	na	1350 (95)	1326 (94)	83 (66)	86 (69)
Black	na	na	113 (1.8)	112 (1.8)	1100 (12.4)	1124 (12.6)	na	na	na	na	na	na
Asian	na	na	**Chinese:** 1854 (29.1) **South Asian:** 927 (14.6) **Other Asian:** 341 (5.4)	**Chinese:** 1837 (29.0) **South Asian:** 927 (14.6) **Other Asian:** 355 (5.6)	na	na	na	na	na	na	Indo-Asian: 28 (22)	Indo-Asian: 20 (16)
other	na	na	96 (1.5)	101 (1.6)	322 (3.6)	312 (3.5)	na	na	na	na	14 (11)	19 (15)

Body mass index, kg/m2	Median (IQR) = 26.4 (23.7, 30.1)	Median (IQR) = 26.8 (24.0, 30.1)	27.15±4.78	27.07±4.77	median (IQR) = 28.3 (25.3–32.0)	median (IQR) = 28.4 (25.3–32.0)	23.8	23.8	28.7	28.8	31.0 ± 6.3	31.0 ± 6.0
Blood pressure — mm Hg												
Systolic	na	na	138.04±14.92	138.06±14.62	Median (IQR) = 134 (124–145)	Median (IQR) = 134 (124–145)	132.0 (16.8)	132.4 (16.8)	144 (15.9)	144 (16.1)	na	na
Diastolic	na	na	81.85±9.38	81.90±9.26	Median (IQR) = 80 (75–87)	Median (IQR) = 80 (75–87)	78.4 (10.4)	78.8 (10.2)	83 (8.5)	83 (8.4)	na	na
Cholesterol - mg/dL												
Total	Median (IQR) = 208.8 (185.6-235.9)	Median (IQR) = 204.95 (185.6-232)	201.5±42.6	201.3±41.7	Median (IQR) = 186 (168–200)	Median (IQR) = 185 (169-199)	242.46	242.46	207.27	206.9	na	na
LDL	Median (IQR) = 123.74 (104.4, 146.95)	Median (IQR) = 123.74 (104.4, 146.95)	127.8±36.1	127.9±36.0	Median (IQR) = 108 (94-119)	Median (IQR) = 108 (94-119)	156.6	156.6	117.56	116.78	na	na
HDL	Median (IQR) = 60.32 (46.4, 73.47)	Median (IQR) = 58.78 (48.34, 71.54)	44.7±13.9	44.9±13.8	Median (IQR) = 49 (40-60)	Median (IQR) = 49 (40-60)	57.62	57.62	53.75	54.91	na	na
Triglycerides - median (IQR) mg/dL	111.6 (79.72 - 159.43)	115.15 (79.72 - 159.43)	128.8 (92.9–179.6)	126.5 (92.9-176.1)	118 (85–169)	118 (86–169)	127.55 (95.66–176.26)	127.55 (94.77–178.92)	150.58 (106.29 - 212.58)	147.92 (103.63 - 212.58)	na	na
Diabetes	na	na	374 (5.9)	357 (5.6)	na	na	804 (21)	828 (21)	na	na	na	na
Hypertension	322 (22)	335 (23)	2403 (37.8)	2411 (38.0)	na	na	1613 (42)	1664 (42)	1193 (84)	1184 (84)	60 (48)	66 (53)
Smoking status – no. (%)												
Current smoker	260 (18)	209 (15)	1740 (27.4)	1784 (28.1)	1400 (15.7)	1420 (16.0)	823 (21)	791 (20)	308 (22)	323 (23)	28 (22)	33 (26)
Ex-smoker	606 (43)	637 (45)	na	na	na	na			622 (44)	601 (43)	na	na
Never smoked	556 (39)	585 (41)	na	na	na	na	na	na	498 (35)	485 (34)	na	na
Family history of premature coronary heart disease	285 (22)	263 (20)	1675 (26.3)	1660 (26.2)	997 (11.2)	1048 (11.8)	na	na	na	na	na	na
Participants with prior CVD (%) Medications, no. (%)	0		0		0		0		0		0	
Aspirin	3 (3)	3 (2)	686 (10.8)	707 (11.1)	1481 (16.6)	1477 (16.6)	36 (1)	42 (1)	221 (15)	207 (15)	na	na
Beta-blocker	na	na	504 (7.9)	516 (8.1)	na	na	318 (8)	329 (8)	219 (15)	237 (17)	na	na
Calcium-channel blocker	na	na	941 (14.8)	944 (14.9)	na	na	1017 (26)	1048 (26)	304 (21)	290 (21)	na	na

Alpha-blocker	na	na	76 (1.2)	65 (1.0)	na	na	na	na	113 (8)	104 (7)	na	na
Diuretics	na	na	39 (0.6)	26 (0.4)	na	na	111 (3)	128 (3)	262 (18)	282 (20)	na	na
ACE inhibitors/ ARB	10 (9)	10 (8)	na	na	na	na	473 (12)	512 (13)	637 (45)	615 (44)	na	na

Table 1: Data are presented as mean ± standard deviation unless otherwise indicated. T.C. = Total cholesterol concentration. IQR = Interquartile range. ACE = angiotensin-converting enzyme. ARB = angiotensin receptor blockers. CVD = cardiovascular disease.

	HYRIM 2004		*PREVEND IT, 2004*		*AFCAPS/TexCAPS, 1998*		*WOSCOPS,1995*	
	Fluvastatin	Placebo	Provastatin	Placebo	Lovastatin	Placebo	pravastatin	Placebo
Intervention	40 mg	na	40 mg	na	20 mg titrated to 40 mg if their LDL-C level was more than 2.84 mmol/L (110 mg/dL)	na	40 mg	na
Country/region	Norway		Netherlands		Texas, United States		Scotland	
Study design	randomized, placebo-controlled, 2 × 2 factorial trial		double-blind, randomized, placebo-controlled, 2 x 2 factorial trial		randomized, double-blind, placebo-controlled trial		Randomized, double-blind, placebo-controlled trial	
n.	142	143	433	431	3304	3301	3302	3293
gender- no. (%)								
male	na	na	67.7%	62.2%	na	na	na	na
female	na	na	na	na	na	na	na	na
Age- years (n)	56.8 ± 8.6	57.5 ± 8.2	52.1±11.9	50.5±11.7	58 (±7)	58 (±7)	55.3±5.5	55.1±5.5
Race or ethnic group — no. (%)								
Hispanic	na	na	na	na	247 (7)	240 (7)	na	na
White	na	na	95.4%	96.8%	2925 (89)	2935 (89)	na	na
Black	na	na	na	na	105 (3)	101 (3)	na	na
Asian	na	na	na	na	na	na	na	na
other	na	na	na	na	na	na	na	na
Body mass index, kg/m2	29.3 ± 2.5	29.0 ± 2.4	26±4	26±4	men = 27.1 (±3.1) ; women = 26.4 (±3.5)	men = 27.0 (±3.0) ; women = 26.4 (±3.8)	26.0±3.2	26.0±3.1
Blood pressure — mm Hg								
Systolic	139.8 ± 15.6	140.5 ± 15.0	131±18	130±17	138 (±17)	138 (±17)	135±18	136±17
Diastolic	88.1 ± 8.3	87.6 ± 8.9	77±10	76±10	78 (±10)	78 (±10)	84±11	84±10
Cholesterol - mg/dL								
Total	225.83± 29	230.1± 35.96	224.3± 38.67	224.3± 38.67	na	na	272±23	272±22
LDL	146.17± 27.07	149.27± 33.2	158.55 ± 38.67	154.68 ± 38.67	na	na	192±17	192±17

HDL	49.11± 11.6	49.88 ± 12.76	38.67 ± 11.6	38.67 ± 15.4	na	na	44±9	44±10
Triglycerides - median (IQR) mg/dL	155 ± 70.86	159.43 ± 80.6	124 (79.72 - 177.15)	115.15 (79.72- 168.3)	na	na	162 ± 70	164 ± 68
Diabetes	na	na	2.80%	2.30%	84 (3.0)	71 (2.0)	41(1)	35(1)
Hypertension	na	na	na	na	719 (22)	729 (22)	531(16)	506(15)
Smoking status – no. (%)								
Current smoker	25 (17.6)	19 (13.3)	42.3%	37.6%	429 (13)	389 (12)	1445 (44)	1460 (44)
Ex-smoker	52 (36.6)	69 (48.3)	31.6%	34.1%	na	na	1138(34)	1127(34)
Never smoked	65 (45.8)	55 (38.5)	na	na	na	na	717(22)	705(21)
Family history of premature coronary heart disease	na	na	na	na	497 (15)	538 (16)	na	na
Participants with prior CVD (%)	0		3.4		0		< 9	
Medications, no. (%)								
Aspirin	na	na	1.4	3.5	571 (17.3)	561 (17.0)	na	na
Beta-blocker	24 (16.9)	30 (21.1)	0.7	1.4	141 (4.3)	156 (4.7)	na	na
Calcium-channel blocker	47 (33.1)	56 (39.4)	0.7	1.2	171 (5.2)	170 (5.1)	na	na
Alpha-blocker	na	na	na	na	68 (2.1)	67 (2.0)	na	na
Diuretics	41 (28.9)	33 (23.2)	0.5	0.9	203 (6.1)	203 (6.1)	na	na
ACE inhibitors/ ARB	46 (32.4)	45 (31.7)	na	na	244 (7.4)	257 (7.8)	na	na

Table 1: Data are presented as mean ± standard deviation unless otherwise indicated. T.C. = Total cholesterol concentration. IQR = Interquartile range. ACE = angiotensin-converting enzyme. ARB = angiotensin receptor blockers. CVD = cardiovascular disease.

METEOR (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin), KAPS (Kuopio Atherosclerosis Prevention Study), and CAIUS (Carotid Atherosclerosis Italian Ultrasound Study) trials had non-clinical outcomes; therefore, they were excluded from our review. ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm), ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), and ASPEN (Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus) trials were excluded since they had less than 90% individuals free of CVD [9,10,29,30-32]. Figure 2 and Figure 3 represent the risk of bias table and graph of the included RCTs, respectively. RCTs included in our review were completely or partially funded by pharma companies. AFCAPS/TexCAPS and HYRIM trials did not give much information about the randomization process. Blinding of the participants was not done in the MEGA trial [23,26,28]. Significant loss to follow-up of study participants was seen in the Beishuizen et al. trial [25]. Furthermore, the MEGA trial did not report all adverse events mentioned in their protocol [23].

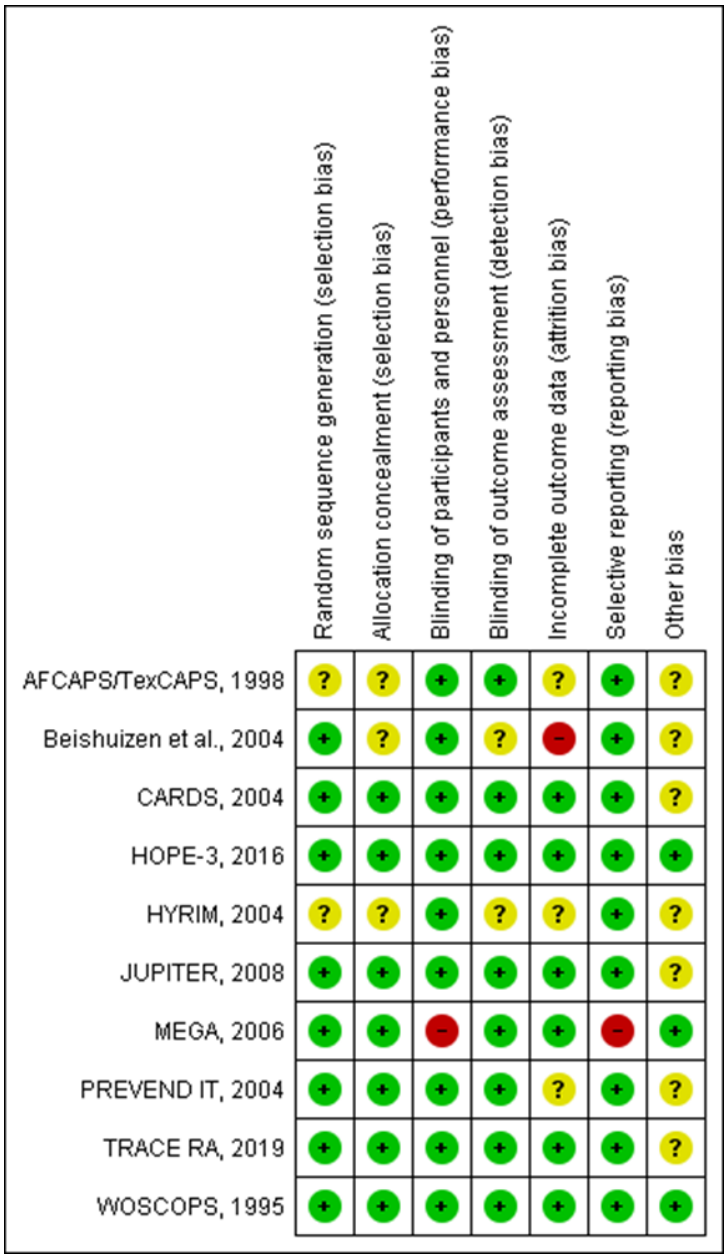

Figure 2: Risk of Bias Table of the RCTs included in the Review as per Cochrane Risk of Bias Assessment Tool.

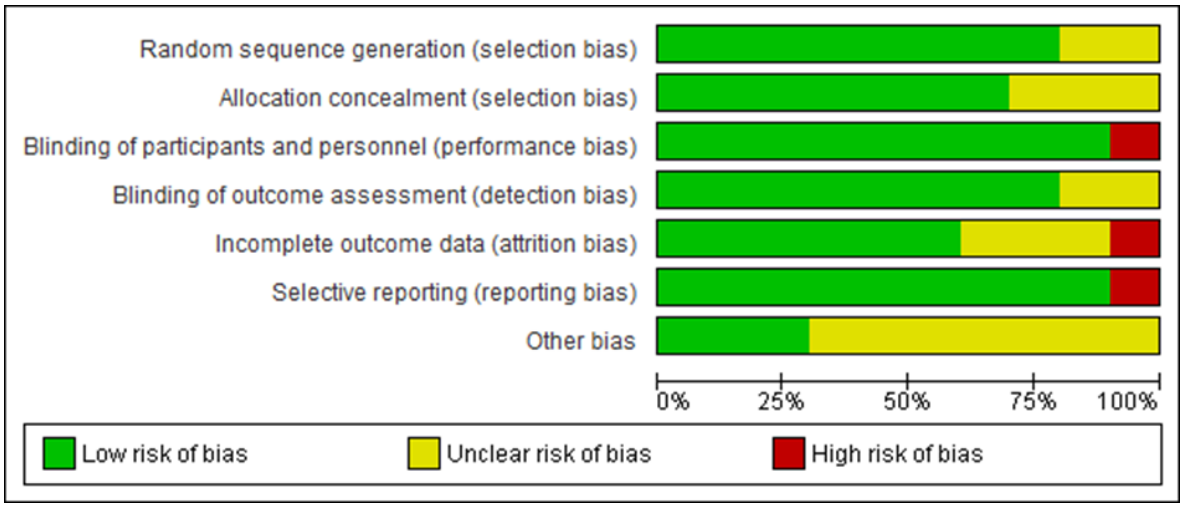

Figure 3: Graph Illustrating the Risk of bias of the RCTs included in the Review as per Cochrane Risk of Bias Assessment Tool.

Table 2 illustrates the primary endpoint of included trials in our study and the amount of change in plasma LDL-C level compared to placebo during different study periods. In Beishuizen et al [25]. RCT, primary and secondary endpoints were non-clinical, and we included other clinical outcomes of the trial in Table 2. HYRIM's primary endpoint was non-clinical, and we included the secondary endpoint of the trial in Table 2 [26]. In the remaining eight RCTs, primary endpoints were clinical and included in Table 2. The primary endpoints of HOPE-3, JUPITER, MEGA, CARDS, AFCAPS/TexCAPS, WOSCOPS, and other clinical outcomes of Beishuizen et al [6,20-25,28]. achieved statistical significance. In these trials, statins lowered the LDL-C value compared to the placebo, which was statistically significant. Hence, we could associate cardiovascular events or mortality reduction with LDL-C reduction by statins in seven clinical trials. The primary endpoints of TRACE RA, PREVEND IT, and the secondary endpoint of HYRIM could not attend to statistical significance [20,26,27]. However, statins lowered LDL-C in these trials that were statistically significant. Finally, we could associate statistically significant cardiovascular events (CVEs) or mortality reduction with absolute LDL-C reduction in seven clinical trials, whereas, in three clinical trials, we could not find the association.

Study	**Primary Endpoint**		**Change in LDL-C level during the study**
	Definition	**Result**	
WOSCOPS,1995 6	First event: non-lethal MI or CHD death.	Statistically significant decrease in the risk of the combined primary endpoints of definite non-lethal MI and CHD mortality (risk reduction 31%, 95% confidence interval [CI]:17-43%, P<0.001).	Pravastatin significantly reduced LDL cholesterol by 26% over the course of the study; The placebo group did not achieve a similar decrease.
TRACE RA, 2019 20	CVEs like MI, Transient Ischemic Attack, nonlethal Ischemic Stroke, non-coronary or coronary revascularization procedures, or cardiovascular death. The primary endpoint excluded non-coronary cardiac death and confirmed cerebral hemorrhage.	24 vs 36 patients had confirmed CVEs in Atorvastatin vs placebo [HR=0.66, 95% CI (0.39-1.11) P= 0.115].	Follow up of 2.51 median years. At the end of the trial, mean LDL-C levels were 0.77 mmol/L lower among the participants receiving atorvastatin in comparison to participants in the placebo group (median 2.59 mg/L [IQR 0.94, 6.08] versus 3.60 mg/L [IQR 1.47, 7.49]; P < 0.0001).
HOPE-3, 2016 [21]	The first coprimary endpoint included a composite of nonlethal MI, cardiovascular death, or nonlethal stroke. The second coprimary endpoint included revascularization procedure, heart failure, and resuscitated cardiac arrest.	First coprimary outcome was HR= 0.76 , 95% CI (0.64-0.91) with the p-value of 0.002 Second coprimary outcome was HR= 0.75, 95% CI (0.64-0.88) with the p-value of <0.001	At one year, there was lower mean LDL-C in the rosuvastatin group by 39.6 mg/dl (1.02 mmol/L) vs. placebo (P<0.001). At three years, it was 34.7 mg/dl (0.90 mmol/L) lower and 29.5 mg/dl (0.76 mmol/L) lower at the end of the trial (overall mean difference, 34.6 mg/dl [0.90 mmol/L] or 26.5%; P<0.001).
JUPITER, 2008 [22]	The primary endpoint includes first CVEs like nonlethal stroke, nonlethal MI, arterial revascularization, unstable angina hospitalization, or cardiovascular death.	At the end of the study, lower CVEs occurred in the rosuvastatin group in comparison to placebo (142 vs. 251) [HR=0.56; 95% CI, 0.46 to 0.69, P<0.00001]	At one year, median LDL-C was 55 mg/dl (1.4 mmol/L) in the rosuvastatin group vs. 110 mg/dl (2.8 mmol/L) in placebo. The rosuvastatin group, as compared with the placebo group, had a 50% lower median LDL-C level (mean difference 47 mg/dl [1.2 mmol/L]; P<0.001).

MEGA, 2006) [23]	The primary composite endpoint was the first occurrence of CHD, i.e., lethal and non-lethal MI, coronary revascularization procedure, angina, cardiac and sudden death.	The incidence of CHD was significantly lower in the diet plus pravastatin group compared to diet alone at 5 years (HR=0.70, 95% CI, 0.50-0.97; P = 0.03) and at the end of study (HR=0.67, 95% CI:0.49-0.91, P=0.01).	During follow-up of mean 5.3 years, LDL-C in the diet plus pravastatin group was 18 % lower than baseline in comparison to 3 % in the diet group (P<0.0001).
CARDS, 2004 [24]	The first of these: Acute CHD event (MI that includes silent infarction, resuscitated cardiac arrest, unstable angina, death due to acute CHD), stroke, or coronary revascularization procedures.	Atorvastatin was associated with a 37% reduction in incidence of major CVEs. Primary Endpoint (HR=0.63, 95% CI ,0.48-0.83; P=0.001)	At one, two, three, and four years, the LDL-C level was reduced with atorvastatin usage compared to placebo group (mean (SD) concentration, 1 year= 0.69 vs. 0.80 mmol/L; 2 years=0.73 vs. 0.82 mmol/L; 3 years=0.71 vs. 0.82 mmol/L; 4 years=0.70 vs. 0.80 mmol/L; P<0.0001).
Beishuizen et al., 2004 [25]	Primary and secondary endpoints were non-clinical. The following predefined CVEs were evaluated during the study: cardiovascular death, nonfatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, nonfatal stroke, peripheral artery bypass graft, percutaneous transluminal angioplasty, or amputation because of atherosclerotic disease.		After two years, LDL-C was decreased by 25% in the cerivastatin group compared to a rise of 8% in the placebo group (p<0.001).
HYRIM, 2004 [26]	Primary Endpoint: Non-Clinical. Secondary outcome variables included MACE (MACE; lethal or nonlethal MI, cardiac death, coronary intervention procedures) and CVD events (lethal or nonlethal acute MI, sudden death, new-onset angina pectoris, hear failure of New York Heart Association Class II-IV, silent MI , lethal or nonlethal stroke, transient ischemic attack). Although the study was not large enough to identify significant differences in outcomes, fluvastatin was associated with fewer cardiac events than the placebo group (11 CVEs vs. 15) or MACE (6 MACEs vs. 9 MACEs with placebo), and total nine patients died during the course of the study (four deaths in fluvastatin vs. five in placebo).		After 3 months of treatment, fluvastatin lowered LDL-C levels by 0.85 mmol/L (from 3.87 to 3.02 mmol/L; P < 0.0001) compared with placebo. The reduction in LDL-C levels compared with placebo after 4 years was 0.49 mmol/L (P < 0.0001), giving an average difference through 4 years of 0.6 mmol/L between treatment groups.
PREVEND IT, 2004 [27]	The combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity. Hospitalization for nonfatal MI or myocardial ischemia, heart failure, peripheral vascular disease, and/or cerebrovascular accident.	Pravastatin group had a 13% lower incidence of primary endpoint than the placebo group (4.8% vs. 5.6%, P=0.649).	Pravastatin lowered LDL-C significantly during follow-up compared to placebo (mean (SD) concentration, 1 year =3.1±0.8 vs. 4.1±1.6 mmol/L ; 2 years = 3.1 ±0.9 vs. 3.9±0.9 mmol/L; 3 years = 3.1±0.9 vs. 4.0±1.0 mmol/L ; 4 years = 3.1 ±0.9 vs. 3.9+0.9 mmol/L; P<0.05).
AFCAPS/TexCAPS, 1998 [28]	Acute major coronary events like lethal or nonlethal MI, sudden cardiac death, or unstable angina.	Primary endpoints RR=0.63, 95% CI (0.50-0.79) (P<0.001). Lovastatin treatment resulted in 37% risk reduction than placebo (cox model 95% CI, 21%-50%; P<0.001).	At one year, lovastatin reduced LDL-C by 25% to 2.96 mmol/L (115 mg/dl) compared to placebo 4.04 mmol/L (156 mg/dl).

MI: myocardial infarction. MACE: major adverse cardiac events. CVE: cardiovascular event. CHD: coronary heart disease. CVD: cardiovascular disease. RR: relative risk.

Table 2 : Endpoints and Results of the Included RCTs.

Discussion

Of the ten RCTs included in this review, seven showed statistically significant clinical benefit in terms of CVEs or mortality measured as H.R. or R.R. These studies were: HOPE-3, JUPITER, MEGA, CARDS, Beishuizen et al., AFCAPS/TexCAPS, and WOSCOPS [6,21-25,28]. Clinical benefits were not only observed in terms of coronary events but also the incidence of stroke, sudden cardiac death, death from CHD, coronary revascularization procedures, arterial revascularization procedures, death from cardiovascular causes, and all-cause mortality (Table 2). Nevertheless, three trials did not reach statistical significance: TRACE RA, HYRIM, and PREVEND IT [20,26,27]. In TRACE RA, because the study was finished earlier due to an unexpected lower occurrence of CVEs, and the H.R. for primary endpoint did not reach statistical significance [20]. Although the fluvastatin group had fewer cardiac events than the placebo group in the HYRIM 26 study, the number of events was insufficient to reveal significant differences between intervention and control groups. Furthermore, although there was a significant reduction in LDL-C concentrations in the PREVEND IT study, pravastatin did not decrease the incidence of the CVEs as compared to the placebo group [27]. However, this study did not exclude the plausibility of a long-term benefit of cholesterol-lowering among the participants.

ASCOT-LLA was a multicenter RCT that satisfied the lipid entry criteria of this review but was not included since none of the participants were free of CVD [30]. However, the findings of this trial were satisfactory to establish the primary preventive effectiveness of statins in those subjects with optimal or borderline cholesterol levels as there was a substantial decrease in major CVEs with atorvastatin despite a shorter surveillance time than planned before the start of the study.

In the JUPITER trial, in contrast to the placebo group, the rate of the first major cardiovascular incident was reduced in the rosuvastatin group (HR=0.56, 95% CI, [0.46-0.69]; P<0.0001) [22]. Among the included trials in this study, JUPITER has the lowest average LDL-C of participants of 108 mg/dl [22]. In the JUPITER trial, rosuvastatin reduced the value of LDL-C by 55 mg/dl at one year [22]. In the WOSCOPS study, the combined primary endpoint of definite nonfatal MI and death from CHD was significantly lower (risk reduction of 31%, 95% CI [17-43%]; P<0.001) [6]. Among the included trials in our study, the WOSCOPS trial has the highest average LDL-C of participants of 192 mg/dl [6]. In the WOSCOPS trial, pravastatin significantly lowered the LDL-C by 26 % throughout the study duration. Similarly, a significant decrease in CVEs and mortality were linked with considerable lowering of LDL-C in other studies such as HOPE-3, MEGA, CARDS, Beishuizen et al., and AFCAPS/TexCAPS [21,23-25,28]. Hence, in seven clinical trials (WOSCOPS, HOPE-3, JUPITER, MEGA, CARDS, Beishuizen et al. , AFCAPS/TexCAPS) where baseline LDL-C was from low to high range, lowering LDL-C was linked to a reduction in the number of cardiovascular events and mortality [6,21-25,28]. Also, in ASCOT-LLA, the statistically significant reduction in CVEs was linked with a significant LDL-C reduction of 43.3 mg/dl in the atorvastatin group [30]. This proves that absolute reduction in LDL-C is crucial for preventing CVEs in those who had no prior CVD and can be achieved at any initial LDL-C level.

Statins were beneficial in decreasing the 5-year incidence of major coronary events, coronary revascularization, and stroke in the Cholesterol Treatment Trialists' (CTT) 2005 study [33]. This study demonstrated that every mmol/L reduction in LDL-C reduced CVEs by roughly one-fifth, regardless of the original lipid profile or other patient variables [33]. According to the CTT 2010 research, every one mmol/L reduction in LDL-C reduces the yearly incidence of vascular events such as myocardial infarction, revascularization procedures, and ischemic stroke by slightly over a fifth [34]. According to the CTT 2010 study, lowering LDL-C by 2-3 mmol/L would cut the risk by another 40-50% [34]. In 2012, CTT collaborators conducted a meta-analysis that demonstrated that reducing LDL-C with statins could significantly reduce the risk of major vascular events, regardless of age, gender, baseline LDL-C, or prior vascular disease, as well as vascular fatality and all-cause mortality [35]. According to CTT 2012 meta-analysis, in individuals with a 5-year risk of major vascular events lower than 10%, a reduction in LDL-C by 1 mmol/L with statin results in an absolute decrease in major vascular events of about 11 per 1000 over 5 years [35]. Although these meta-analyses included both primary and secondary CVD prevention trials of statins, these analyses correlated the relation between absolute LDL-C reduction and prevention of ASCVD [33-35]. When findings of CTT 2005, CTT 2010, and CTT 2012 are taken into account with the findings of Table 2, we can associate absolute LDL-C reduction achieved by statins with primary prevention f CVD and mortality [33-35]. Hence, further research is needed where one can relate baseline serum LDL-C level, absolute LDL-C reduction and percentage of reduction of CVEs, mortality in both statins and control groups in populations who had no prior CVD. It is better to look at a 3-axis plot of CVEs reduction (Y-axis) versus absolute LDL-C reduction (X-axis) versus baseline LDL-C level (Z-axis). This 3-plot axis graph will provide the definitive quantitative evidence of the role of absolute reduction of LDL-C and primary prevention of CVD, mortality with statins.

The addition of evolocumab, a PCSK9 inhibitor to statin treatment, has decreased LDL-C levels by 59% from baseline in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition Subjects with Elevated Risk) study when compared to placebo [36]. In the FOURIER study, lowering LDL-C from 92 mg/dl to 30 mg/dl significantly decreased the risk of cardiovascular events while having no significant overall adverse events [36]. The addition of ezetimibe to statin therapy reduced LDL-C from 70 mg/dl to 54 mg/dl in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial, which was associated with a substantial reduction in major CVEs without significant adverse events [37]. As a result, even though the patients in the IMPROVE-IT study had LDL-C in the lower range, lowering LDL-C by ezetimibe and statin combination therapy significantly decreased major CVEs [37]. It is apparent from the outcomes of the FOURIER and IMPROVE-IT studies that decreasing LDL-C has a benefit even

if the baseline LDL-C is in the lower levels [36,37]. Also, statins' benefit is enhanced when used in combination therapy with ezetimibe or evolocumab since it produced greater LDL-C reduction.

In 2019, European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) statin eligibility criteria to start statin for primary prevention of CVD, the LDL-C in lipid-based criteria was decreased from 232 mg/dl to 190 mg/dl compared to the 2016 ECS/EAS guideline [38]. Similarly, in risk-based criteria for those with SCORE (Systematic Coronary Risk Evaluation) between 5 % to < 10%, the LDL-C threshold was lowered to 100 mg/dl from 155 mg/dl, and for SCORE ≥ 10%, the threshold was lowered to 70 mg/dl from 100 mg/dl in comparison to 2016 ESC/EAS guideline. With the 2019 ESC/EAS recommendation reducing the LDL-C threshold for initiating statins, the number of people eligible for primary ASCVD prevention with statins has almost doubled. In the general population, the 2019 ESC/EAS guideline offers a higher potential for ASCVD prevention than the 2016 ECS/EAS guideline, which has a similar NNT to the 2016 guideline for preventing one cardiovascular event [38].

Individuals aged 20 to 75 years old with LDL-C ≥190 mg/dl were recommended to use high-intensity statins without risk evaluation for the primary CVD prevention, as per the 2019 American College of Cardiology and American Heart Association (ACC/AHA) guideline [39]. Nevertheless, this threshold might be seen as very high in light of the current evidence that suggests the risk of CVD persists independently from any specific baseline LDL-C levels. Indeed, our study shows that populations with mean levels of LDL-C between 108 and 192 mg/dl were benefited from statins with reduced CVEs, and in all these populations, a certain reduction of LDL-C level was evident. A meta-analysis conducted by Singh et al. showed that statins could prevent CVD and revascularization procedures at the LDL-C range from 100 to 159 mg/dl without any significant adverse events [17]. However, following the threshold of ≥190 mg/dl, it seems that the populations with LDL-C less than 190 mg/dl may be prevented from the benefits of statins. Besides, if there is a family history of early ASCVD and LDL-C ≥ 160 mg/dl, the 2019 ACC/AHA guideline recommends initiating statin treatment for primary CVD prevention in those aged 20 to 39 years [39]. However, Singh et al.'s meta-analysis demonstrated that the usage of statins is still beneficial for LDL-C below 160 mg/dl [17]. Furthermore, prior research has revealed that the connection between serum cholesterol levels and CHD risk factors can be continuously graded without any specific threshold value [12,16]. Following the 2019 ACC/AHA guideline, it is evident that patients aged 20-39 years will be prevented from benefiting from statin therapy if they do not have a family history of premature ASCVD and their LDL-C is more than 160 mg/dl. Therefore, we believe that primary preventive guidelines should focus rather on absolute LDL-C reduction. In patients with no history of CVD, we were able to associate absolute LDL-C reduction with statins to the prevention of CVD and death. We found a positive association between the amount of decrease in LDL-C levels with a reduced risk of CVD and mortality, despite the three clinical trials (TRACE RA, HYRIM, and PREVEND IT) that did not produce significant results, for their inadequate surveillance and sample size [20,26,27]. According to the FOURIER trial, IMPROVE-IT trial, and Singh et al. meta-analysis, the benefit of lowering LDL-C exists even at low LDL-C levels [17,36,37].

Limitations

In our systematic review, we generated the hypothesis where we associated absolute LDL-C reduction with primary prevention of Atherosclerotic Cardiovascular Disease. The major limitation in our systematic review is that we had to rely on LDL-C data from RCTs of statins for the primary prevention of cardiovascular disease and mortality at different periods of study. The decrease in LDL-C level achieved at the end of some of the statin clinical trials included in this review was not reported. Hence, it is difficult to maintain uniformity in comparison. In addition, statins have "cholesterol-independent" or "pleiotropic" effects that provide further cardiovascular event protection. So, it is evident that the sole benefit of statins could not just be attributed to cholesterol-lowering. Thus, the clinical trials included in our systematic review could not address this issue. Therefore, future primary preventive clinical trials of statins to prevent cardiovascular disease and mortality should measure the benefit of statins' cholesterol-dependent and cholesterol-independent effects.

Conclusion

There is a positive association between the amount of decrease in LDL-C level and the prevention of CVEs and mortality in those who had no prior CVD despite high to low mean baseline LDL-C. Although there are several thresholds of LDL-C for commencing statin therapy to prevent ASCVD in 2019 ESC/EAS and 2019 ACC/AHA primary preventive guidelines, the benefit of lowering LDL-C exists at both high and low baseline LDL-C levels. Therefore, primary preventive guidelines of statins should focus on the amount of LDL-C reduction that is more predictable of the benefit of statins in reducing CVEs and mortality rather than baseline LDL-C level. Further research that could quantify a specific LDL-C reduction with a percentage reduction of CVEs and mortality in those with no prior CVD is necessary. Evidence from such research would help the primary preventive guidelines of statins in targeting to achieve a certain amount of LDL-C reduction to prevent CVEs depending on cardiovascular risk factors present in an individual.

Data Availability

The supporting data for this systematic review has been cited.

Acknowledgments

We want to acknowledge Dr. Sanjay S. Srivatsa (Department of Cardiovascular Diseases and Vascular Medicine, Heart Artery and Vein Center of Fresno, Fresno, United States of America), Dr. Sijan Khatiwada (Angeles University Foundation

School of Medicine, Philippines), Dr. Jack Michel (Larkin Community Hospital, United States of America) and Dr. Donald Hathaway III (Lincoln Medical Center, United States of America) for their guidance in completing this review.

Supplementary Materials

There are three supplementary materials. The first one is the "PRISMA 2020 Checklist," and the second one is "Search strategies in electronic databases used for articles search." The third supplementary file is "Search results." (Supplementary Materials).

Compliance with ethical standards

Conflict-of-Interest Statement: The authors declare no conflict of interest for this article.

Funding: None

References

1. Buhaescu, I., & Izzedine, H. (2007). Mevalonate pathway: a review of clinical and therapeutical implications. Clinical biochemistry, 40(9-10), 575-584.
2. Wierzbicki, A. S., Poston, R., & Ferro, A. (2003). The lipid and non-lipid effects of statins. Pharmacology & therapeutics, 99(1), 95-112.
3. Thavendiranathan, P., Bagai, A., Brookhart, M. A., & Choudhry, N. K. (2006). Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Archives of internal medicine, 166(21), 2307-2313.
4. Brugts, J. J., Yetgin, T., Hoeks, S. E., Gotto, A. M., Shepherd, J., Westendorp, R. G. J., ... & Deckers, J. W. (2009). The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. Bmj, 338.
5. Mills, E. J., Rachlis, B., Wu, P., Devereaux, P. J., Arora, P., & Perri, D. (2008). Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. Journal of the American College of Cardiology, 52(22), 1769-1781.
6. Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., Macfarlane, P. W., ... & Packard, C. J. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New England Journal of Medicine, 333(20), 1301-1308.
7. Kyushu Lipid Intervention Study Group. (2000). Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. Journal of atherosclerosis and thrombosis, 7(2), 110-121.
8. Bruckert, E., Lièvre, M., Giral, P., Crepaldi, G., Masana, L., Vrolix, M., ... & Dejager, S. (2003). Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. The American journal of geriatric cardiology, 12(4), 225-231.
9. Mercuri, M., Bond, M. G., Sirtori, C. R., Veglia, F., Crepaldi, G., Feruglio, F. S., ... & Ventura, A. (1996). Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic Mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. The American journal of medicine, 101(6), 627-634.
10. Salonen, R., Nyyssönen, K., Porkkala, E., Rummukainen, J., Belder, R., Park, J. S., & Salonen, J. T. (1995). Kuopio Atherosclerosis Prevention Study (KAPS) A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation, 92(7), 1758-1764.
11. Heljić, B., Velija-Ašimi, Z., & Kulić, M. (2009). The statins in prevention of coronary heart diseases in type 2 diabetics. Bosnian Journal of Basic Medical Sciences, 9(1), 71.
12. Stamler, J., Wentworth, D., & Neaton, J. D. (1986). Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?: findings in 356 222 primary screenees of the multiple risk factor intervention trial (mrfit). Jama, 256(20), 2823-2828.
13. Rose, G., & Shipley, M. (1986). Plasma cholesterol concentration and death from coronary heart disease: 10 year results of the Whitehall study. Br Med J (Clin Res Ed), 293(6542), 306-307.
14. YANO, K., REED, D. M., & McGEE, D. L. (1984). Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to biologic and lifestyle characteristics. American journal of epidemiology, 119(5), 653-666.
15. Pooling Project Research Group. (1978). Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. Journal of chronic diseases, 31(4), 201-306.
16. Chen, Z., Peto, R., Collins, R., MacMahon, S., Lu, J., & Li, W. (1991). Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. British Medical Journal, 303(6797), 276-282.
17. Singh, B. M., Lamichhane, H. K., Srivatsa, S. S., Adhikari, P., Kshetri, B. J., Khatiwada, S., & Shrestha, D. B. (2020). Role of statins in the primary prevention of atherosclerotic cardiovascular disease and mortality in the population with mean cholesterol in the near-optimal to borderline high range: a systematic review and meta-analysis. Advances in preventive medicine, 2020(1), 6617905.
18. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj, 372.
19. Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj, 366.

20. Kitas, G. D., Nightingale, P., Armitage, J., Sattar, N., Belch, J. J., Symmons, D. P., ... & Isdale, A. (2019). A multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. Arthritis & rheumatology, 71(9), 1437-1449.
21. Yusuf, S., Bosch, J., Dagenais, G., Zhu, J., Xavier, D., Liu, L., ... & Lonn, E. (2016). Cholesterol lowering in intermediate-risk persons without cardiovascular disease. New England Journal of Medicine, 374(21), 2021-2031.
22. Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto Jr, A. M., Kastelein, J. J., ... & Glynn, R. J. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England journal of medicine, 359(21), 2195-2207.
23. Nakamura, H., Arakawa, K., Itakura, H., Kitabatake, A., Goto, Y., Toyota, T., ... & Ohashi, Y. (2006). Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. The Lancet, 368(9542), 1155-1163.
24. Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. W., Livingstone, S. J., ... & Fuller, J. H. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. The Lancet, 364(9435), 685-696.
25. Beishuizen, E. D., Van De Ree, M. A., Jukema, J. W., Tamsma, J. T., Van Der Vijver, J. C. M., Meinders, A. E., ... & Huisman, M. V. (2004). Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. Diabetes care, 27(12), 2887-2892.
26. Anderssen, S. A., Hjelstuen, A. K., Hjermann, I., Bjerkan, K., & Holme, I. (2005). Fluvastatin and lifestyle modification for reduction of carotid intima–media thickness and left ventricular mass progression in drug-treated hypertensives. Atherosclerosis, 178(2), 387-397.
27. Asselbergs, F. W., Diercks, G. F., Hillege, H. L., van Boven, A. J., Janssen, W. M., Voors, A. A., ... & van Gilst, W. H. (2004). Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation, 110(18), 2809-2816.
28. Downs, J. R., Clearfield, M., Weis, S., Whitney, E., Shapiro, D. R., Beere, P. A., ... & Gotto Jr, A. M. (1998). for the AFCAPS/TexCAPS Research Group: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. Jama, 279(20), 1615-1622.
29. Crouse, J. R., Raichlen, J. S., Riley, W. A., Evans, G. W., Palmer, M. K., O'Leary, D. H., ... & METEOR Study Group. (2007). Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. Jama, 297(12), 1344-1353.
30. Sever, P. S., Dahlöf, B., Poulter, N. R., Wedel, H., Beevers, G., Caulfield, M., ... & Östergren, J. (2003). Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. The Lancet, 361(9364), 1149-1158.
31. Allhat, O. (2002). ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). Jama, 288(23), 2998-3007.
32. Knopp, R. H., d'Emden, M., Smilde, J. G., Pocock, S. J., & ASPEN Study Group. (2006). Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes care, 29(7), 1478-1485.
33. Baigent, C. (2005). Cholesterol Treatment Trialists'(CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 366, 1267-1278.
34. Trialists, C. T. (2010). '(CTT) Collaboration, Baigent C, Black-well L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL-cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. 376(9753):1670-1681.
35. Mihaylova, B., Emberson, J., Blackwell, L., Keech, A., Simes, J., Barnes, E. H., ... & Baigent, C. (2012). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet (London, England), 380(9841), 581-590.
36. Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., ... & Pedersen, T. R. (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. New England journal of medicine, 376(18), 1713-1722.
37. Cannon, C. P., Blazing, M. A., Giugliano, R. P., McCagg, A., White, J. A., Theroux, P., ... & Califf, R. M. (2015). Ezetimibe added to statin therapy after acute coronary syndromes. New England Journal of Medicine, 372(25), 2387-2397.
38. Mortensen, M. B., & Nordestgaard, B. G. (2020). 2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease. European heart journal, 41(31), 3005-3015.
39. Arnett DK, Blumenthal RS, Albert MA, et al. 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 [published correction appears in Circulation. 2019 Sep 10;140(11):e649-e650] [published correction appears in Circulation. 2020 Jan 28;141(4):e60] [published correction appears in Circulation. 2020 Apr 21;141(16):e774]. Circulation. 2019;140(11):e596-e646.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2, 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3, 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g.	

		subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7 to 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9 to 11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7 to 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11 to 13
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	13, 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Material 1: PRISMA 2020 Checklist

Electronic databases	Search Strategy
PubMed Central (PMC)	(((hydroxymethylglutaryl-coa reductase inhibitors[MeSH Terms]) OR (simvastatin[MeSH Terms]) OR (lovastatin[MeSH Terms]) OR (pravastatin[MeSH Terms]) OR (atorvastatin[MeSH Terms]) OR (cerivastatin[All Fields]) OR (fluvastatin[MeSH Terms]) OR (rosuvastatin calcium[MeSH Terms]) OR (pitavastatin[All Fields]) OR (Statin[All Fields])) AND ((coronary artery disease[MeSH Terms]) OR (heart diseases[MeSH Terms]) OR (coronary disease[MeSH Terms]) OR (cardiovascular diseases[MeSH Terms]) OR (myocardial infarction[MeSH Terms]) OR (cerebrovascular disorders[MeSH Terms]) OR (stroke[MeSH Terms]) OR (angina pectoris[MeSH Terms]) OR (ischemic attack, transient[MeSH Terms]) OR (mortality[MeSH Terms])) AND ((randomized controlled trials as topic[MeSH Terms]) OR (controlled clinical trials as topic[MeSH Terms]) OR (random allocation[MeSH Terms]) OR (randomly[All Fields]) OR (clinical trials as topic[MeSH Terms]) OR (placebos[MeSH Terms]) OR (primary prevention[MeSH Terms]) OR (cholesterol[MeSH Terms]) OR (cholesterol, ldl[MeSH Terms]))))
PubMed	(((hydroxymethylglutaryl-coa reductase inhibitors[MeSH Terms]) OR (simvastatin[MeSH Terms]) OR (lovastatin[MeSH Terms]) OR (pravastatin[MeSH Terms]) OR (atorvastatin[MeSH Terms]) OR (cerivastatin[All Fields]) OR (fluvastatin[MeSH Terms]) OR (rosuvastatin calcium[MeSH Terms]) OR (pitavastatin[All Fields]) OR (statin[Text Word])) AND ((coronary artery disease[MeSH Terms]) OR (heart diseases[MeSH Terms]) OR (coronary disease[MeSH Terms]) OR (cardiovascular diseases[MeSH Terms]) OR (myocardial infarction[MeSH Terms]) OR (cerebrovascular disorders[MeSH Terms]) OR (stroke[MeSH Terms]) OR (ischemic attack, transient[MeSH Terms]) OR (angina pectoris[MeSH Terms]) OR (mortality[MeSH Terms]) OR (primary prevention[MeSH Terms]) OR (cholesterol[MeSH Terms]) OR (cholesterol, ldl[MeSH Terms]) OR (placebos[MeSH Terms])))
Cochrane Library	#1 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
	#2 MeSH descriptor: [Simvastatin] explode all trees
	#3 MeSH descriptor: [Lovastatin] explode all trees
	#4 MeSH descriptor: [Pravastatin] explode all trees
	#5 MeSH descriptor: [Atorvastatin] explode all trees
	#6 MeSH descriptor: [Fluvastatin] explode all trees
	#7 MeSH descriptor: [Rosuvastatin Calcium] explode all trees
	#8 (cerivastatin)
	#9 (pitavastatin)
	#10 (statins)
	#11 MeSH descriptor: [Coronary Artery Disease] explode all trees
	#12 MeSH descriptor: [Coronary Disease] explode all trees
	#13 MeSH descriptor: [Cardiovascular Diseases] explode all trees
	#14 MeSH descriptor: [Heart Diseases] explode all trees
	#15 MeSH descriptor: [Cardiovascular Abnormalities] explode all trees
	#16 MeSH descriptor: [Myocardial Infarction] explode all trees
	#17 MeSH descriptor: [Cerebrovascular Disorders] explode all trees
	#18 MeSH descriptor: [Stroke] explode all trees
	#19 MeSH descriptor: [Angina Pectoris] explode all trees
	#20 MeSH descriptor: [Ischemic Attack, Transient] explode all trees
	#21 MeSH descriptor: [Mortality] explode all trees
	#22 MeSH descriptor: [Multicenter Studies as Topic] explode all trees
	#23 MeSH descriptor: [Controlled Clinical Trials as Topic] explode all trees
	#24 MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees
	#25 MeSH descriptor: [Clinical Trials as Topic] explode all trees
	#26 MeSH descriptor: [Random Allocation] explode all trees
	#27 MeSH descriptor: [Placebos] explode all trees

	#28 MeSH descriptor: [Primary Prevention] explode all trees
	#29 MeSH descriptor: [Cholesterol] explode all trees
	#30 MeSH descriptor: [Cholesterol, LDL] explode all trees
	#31 ((# 1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) AND (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) AND (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)) with Publication Year from 1994 to 2020, in Trials
Google Scholar	With all of the words: Primary prevention, Statins, Hydroxymethylglutaryl CoA inhibitors, Cardiovascular disease events, Stroke, Myocardial infarction, angina pectoris, Mortality, Coronary artery disease, Randomized Controlled Trial, Clinical Trial, Cholesterol, LDL, Placebo With the exact phrase: primary prevention With at least one of the words: simvastatin, lovastatin, pravastatin, atorvastatin, cerivastatin, fluvastatin, rosuvastatin, pitavastatin, heart diseases, coronary disease, cerebrovascular disorders, cardiovascular disorders, cardiovascular abnormalities, Coronary deaths, transient ischemic attack, random allocation, randomly Where my words occur: anywhere in the article Return articles dated between: 1994-2020

Supplementary Material 2: Search strategies in electronic databases used for articles search

Search results

• PubMed: 4911

(((hydroxymethylglutaryl-coa reductase inhibitors[MeSH Terms]) OR (simvastatin[MeSH Terms]) OR (lovastatin[MeSH Terms]) OR (pravastatin[MeSH Terms]) OR (atorvastatin[MeSH Terms]) OR (cerivastatin[All Fields]) OR (fluvastatin[MeSH Terms]) OR (rosuvastatin calcium[MeSH Terms]) OR (pitavastatin[All Fields]) OR (statin[Text Word])) AND ((coronary artery disease[MeSH Terms]) OR (heart diseases[MeSH Terms]) OR (coronary disease[MeSH Terms]) OR (cardiovascular diseases[MeSH Terms]) OR (myocardial infarction[MeSH Terms]) OR (cerebrovascular disorders[MeSH Terms]) OR (stroke[MeSH Terms]) OR (ischemic attack, transient[MeSH Terms]) OR (angina pectoris[MeSH Terms]) OR (mortality[MeSH Terms]) OR (primary prevention[MeSH Terms]) OR (cholesterol[MeSH Terms]) OR (cholesterol, ldl[MeSH Terms]) OR (placebos[MeSH Terms])))

https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28hydroxymethylglutaryl-coa+reductase+inhibitors%5BMeSH+Terms%5D%29+OR+%28simvastatin%5BMeSH+Terms%5D%29+OR+%28lovastatin%5BMeSH+Terms%5D%29+OR+%28pravastatin%5BMeSH+Terms%5D%29+OR+%28atorvastatin%5BMeSH+Terms%5D%29+OR+%28cerivastatin%5BAll+Fields%5D%29+OR+%28fluvastatin%5BMeSH+Terms%5D%29+OR+%28rosuvastatin+calcium%5BMeSH+Terms%5D%29+OR+%28pitavastatin%5BAll+Fields%5D%29+OR+%28statin%5BText+Word%5D%29%29+AND+%28%28coronary+artery+disease%5BMeSH+Terms%5D%29+OR+%28heart+diseases%5BMeSH+Terms%5D%29+OR+%28coronary+disease%5BMeSH+Terms%5D%29+OR+%28cardiovascular+diseases%5BMeSH+Terms%5D%29+OR+%28myocardial+infarction%5BMeSH+Terms%5D%29+OR+%28cerebrovascular+disorders%5BMeSH+Terms%5D%29+OR+%28stroke%5BMeSH+Terms%5D%29+OR+%28ischemic+attack%2C+transient%5BMeSH+Terms%5D%29+OR+%28angina+pectoris%5BMeSH+Terms%5D%29+OR+%28mortality%5BMeSH+Terms%5D%29+OR+%28primary+prevention%5BMeSH+Terms%5D%29+OR+%28cholesterol%5BMeSH+Terms%5D%29+OR+%28cholesterol%2C+ldl%5BMeSH+Terms%5D%29+OR+%28placebos%5BMeSH+Terms%5D%29%29%29&filter=simsearch1.fha&filter=simsearch3.fft&filter=pubt.clinicalstudy&filter=pubt.clinicaltrial&filter=pubt.controlledclinicaltrial&filter=pubt.multicenterstudy&filter=pubt.randomizedcontrolledtrial&filter=species.humans&filter=age.alladult&filter=years.1994-2020

2. PMC: 5362

(((hydroxymethylglutaryl-coa reductase inhibitors[MeSH Terms]) OR (simvastatin[MeSH Terms]) OR (lovastatin[MeSH Terms]) OR (pravastatin[MeSH Terms]) OR (atorvastatin[MeSH Terms]) OR (cerivastatin[All Fields]) OR (fluvastatin[MeSH Terms]) OR (rosuvastatin calcium[MeSH Terms]) OR (pitavastatin[All Fields]) OR (Statin[All Fields])) AND ((coronary artery disease[MeSH Terms]) OR (heart diseases[MeSH Terms]) OR (coronary disease[MeSH Terms]) OR (cardiovascular diseases[MeSH Terms]) OR (myocardial infarction[MeSH Terms]) OR (cerebrovascular disorders[MeSH Terms]) OR (stroke[MeSH Terms]) OR (angina pectoris[MeSH Terms]) OR (ischemic attack, transient[MeSH Terms]) OR (mortality[MeSH Terms])) AND ((randomized controlled trials as topic[MeSH Terms]) OR (controlled clinical trials as topic[MeSH Terms]) OR (random allocation[MeSH Terms]) OR (randomly[All Fields]) OR (clinical trials as topic[MeSH Terms]) OR (placebos[MeSH Terms]) OR (primary prevention[MeSH Terms]) OR (cholesterol[MeSH Terms]) OR (cholesterol, ldl[MeSH Terms])))

https://www.ncbi.nlm.nih.gov/pmc/?term=(((hydroxymethylglutaryl-coa+reductase+inhibitors%5BMeSH+Terms%5D)+OR+(simvastatin%5BMeSH+Terms%5D)+OR+(lovastatin%5BMeSH+Terms%5D)+OR+-

(pravastatin%5BMeSH+Terms%5D)+OR+(atorvastatin%5BMeSH+Terms%5D)+OR+(cerivastatin%5BAll+Fields%5D)+OR+(fluvastatin%5BMeSH+Terms%5D)+OR+(rosuvastatin+calcium%5BMeSH+Terms%5D)+OR+(pitavastatin%5BAll+Fields%5D)+OR+(Statin%5BAll+Fields%5D))+AND+((coronary+artery+disease%5BMeSH+Terms%5D)+OR+(heart+diseases%5BMeSH+Terms%5D)+OR+(coronary+disease%5BMeSH+Terms%5D)+OR+(cardiovascular+diseases%5BMeSH+Terms%5D)+OR+(myocardial+infarction%5BMeSH+Terms%5D)+OR+(cerebrovascular+disorders%5BMeSH+Terms%5D)+OR+(stroke%5BMeSH+Terms%5D)+OR+(angina+pectoris%5BMeSH+Terms%5D)+OR+(ischemic+attack%2C+transient%5BMeSH+Terms%5D)+OR+(mortality%5BMeSH+Terms%5D))+AND+((randomized+controlled+trials+as+topic%5BMeSH+Terms%5D)+OR+(controlled+clinical+trials+as+topic%5BMeSH+Terms%5D)+OR+(random+allocation%5BMeSH+Terms%5D)+OR+(randomly%5BAll+Fields%5D)+OR+(clinical+trials+as+topic%5BMeSH+Terms%5D)+OR+(placebos%5BMeSH+Terms%5D)+OR+(primary+prevention%5BMeSH+Terms%5D)+OR+(cholesterol%5BMeSH+Terms%5D)+OR+(cholesterol%2C+ldl%5BMeSH+Terms%5D)))

3. Cochrane Library: 5002
Search Name: Real statin search
Date Run: 06/01/2021 03:25:59
Comment: mortality

ID	Search	Hits
#1	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	3447
#2	MeSH descriptor: [Simvastatin] explode all trees	1796
#3	MeSH descriptor: [Lovastatin] explode all trees	2158
#4	MeSH descriptor: [Pravastatin] explode all trees	1005
#5	MeSH descriptor: [Atorvastatin] explode all trees	1697
#6	MeSH descriptor: [Fluvastatin] explode all trees	326
#7	MeSH descriptor: [Rosuvastatin Calcium] explode all trees	1078
#8	(cerivastatin)	194
#9	(pitavastatin)	500
#10	(statins)	5562
#11	MeSH descriptor: [Coronary Artery Disease] explode all trees	6357
#12	MeSH descriptor: [Coronary Disease] explode all trees	13632
#13	MeSH descriptor: [Cardiovascular Diseases] explode all trees	105946
#14	MeSH descriptor: [Heart Diseases] explode all trees	51745
#15	MeSH descriptor: [Cardiovascular Abnormalities] explode all trees	2490
#16	MeSH descriptor: [Myocardial Infarction] explode all trees	11009
#17	MeSH descriptor: [Cerebrovascular Disorders] explode all trees	14856
#18	MeSH descriptor: [Stroke] explode all trees	9502
#19	MeSH descriptor: [Angina Pectoris] explode all trees	4547
#20	MeSH descriptor: [Ischemic Attack, Transient] explode all trees	743
#21	MeSH descriptor: [Mortality] explode all trees	12929
#22	MeSH descriptor: [Multicenter Studies as Topic] explode all trees	1878
#23	MeSH descriptor: [Controlled Clinical Trials as Topic] explode all trees	14466
#24	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	14329
#25	MeSH descriptor: [Clinical Trials as Topic] explode all trees	47714
#26	MeSH descriptor: [Random Allocation] explode all trees	20599
#27	MeSH descriptor: [Placebos] explode all trees	23914
#28	MeSH descriptor: [Primary Prevention] explode all trees	4037
#29	MeSH descriptor: [Cholesterol] explode all trees	10083
#30	MeSH descriptor: [Cholesterol, LDL] explode all trees	4679
#31	((# 1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) AND (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) AND (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)) with Publication Year from 1994 to 2020, in Trials	5002

4. Google Scholar: 1297
Advanced Search
Find articles
with all of the words: Primary prevention Statins hydroxymethylglutaryl coa inhibitors Cardiovascular disease events Stroke Myocardial infarction angina pectoris Mortality Coronary artery disease Randomized Controlled Trial Clinical Trial Cholesterol LDL Placebo
with the exact phrase: primary prevention
with at least one of the words: simvastatin lovastatin pravastatin atorvastatin cerivastatin fluvastatin rosuvastatin pitavastatin heart diseases coronary disease cerebrovascular disorders cardiovascular disorders cardiovascular abnormalities Coronary deaths transient ischemic attack random allocation randomly
where my words occur: anywhere in the article

Return articles dated between: 1994-2020

https://scholar.google.com/scholar?as_q=Primary+prevention+Statins+hydroxymethylglutaryl+coa+inhibitors+-Cardiovascular+disease+events+Stroke+Myocardial+infarction+angina+pectoris+Mortality+Coronary+artery+disease+Randomized+Controlled+Trial+Clinical+Trial+Cholesterol+LDL+Placebo&as_epq=Primary+prevention&as_oq=simvastatin++lovastatin++pravastatin++atorvastatin++cerivastatin++fluvastatin++rosuvastatin+++pitavastatin+++heart+diseases++coronary+disease++++cerebrovascular+disorders+cardiovascular+disorders+cardiovascular+abnormalities+Coronary+deaths++transient+ischemic+attack++++++random+allocation++randomly+++++&as_eq=&as_occt=any&as_sauthors=&as_publication=&as_ylo=1994&as_yhi=2020&hl=en&as_sdt=0%2C5