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The Effectiveness of Statins for Primary Prevention: A Rapid Review

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Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy makers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

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To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

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Table of Contents

List of Abbreviations

CVD	Cardiovascular disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
RCT	Randomized controlled trial

Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit www.hqontario.ca.

Objective of Analysis

The objective was to determine the effectiveness of statins in avoiding downstream adverse clinical outcomes associated with dyslipidemia, specifically major coronary events and stroke.

Clinical Need and Target Population

Dyslipidemia

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide. (1) An estimated 42% of CVD deaths are attributed to myocardial infarction, and another one-third to stroke. (2) Dyslipidemias, including elevated blood cholesterol, promote the process of atherosclerosis and are a metabolic risk factor for CVD. Left untreated, high cholesterol can progress into ischemic heart disease, coronary artery disease and myocardial infarction, cerebrovascular disease and stroke, and peripheral vascular diseases. (1) Total cholesterol is mainly comprised of high- and low-density lipoprotein cholesterol (HDL and LDL, respectively) which have opposite influences on risk of CVD, the latter elevating risk. (3) Given this association, lowering cholesterol levels, specifically LDL, is a primary treatment goal for patients with dyslipidemia.

Technology/Technique

Although LDL cholesterol levels can be modified through changes in diet and lifestyle, pharmacotherapy is the cornerstone of treatment, with statins as the first choice. Statins act via competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibits an early rate-limiting step in hepatic cholesterol biosynthesis. (4) Health Canada has approved several statins in the last few decades, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. (5) Statins are generally well tolerated and effective in secondary prevention, slowing atherosclerosis and reducing myocardial infarctions and stroke in patients with coronary artery disease. (6) In the context of primary prevention, however, results have been mixed and interpretations around the effectiveness in preventing adverse clinical outcomes have varied.

Rapid Review

Research Question

Are statins effective in preventing the adverse clinical effects of dyslipidemias, specifically major coronary events and stroke?

Research Methods

Literature Search

A literature search was performed on December 5, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, until December 5, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-text reports
- published between January 1, 2008, and December 5, 2012
- systematic reviews, meta-analyses, and health technology assessments
- studies on primary prevention of cardiovascular diseases with statins

Exclusion Criteria

- randomized controlled trials (RCTs), editorials, case studies, observational studies, or commentaries
- secondary prevention of cardiovascular disease or stroke
- cost-effectiveness and other economic analyses
- comparisons of the effectiveness of particular statins against one another

Outcomes of Interest

- stroke events (i.e., fatal and nonfatal)
- major coronary events (e.g., myocardial infarction, coronary death)

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (7) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (7) For more detailed information, please refer to the latest series of GRADE articles. (7)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Literature Search

The database search yielded 470 citations published between January 1, 2008, and December 5, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Three meta-analyses met the inclusion criteria. (8-10) According to the AMSTAR evaluation of methodological quality, the reviews by Brugts et al, (8) Mills et al, (9) and Taylor et al (10) scored 8, 8, and 11 out of 11, respectively (see Appendix 2). In consideration of the superior methodological quality, recency, and the comparatively stringent inclusion criteria for primary prevention study populations (Table 1), the review by Taylor et al (10) is the focus of the results, with those by Mills et al (9) and Brugts et al (8) providing additional data and discussion.

Table 1: Meta-Analyses Examining the Effectiveness of Statins for Primary Prevention of Cardiovascular Disease

Author	Year	Authors' Primary Prevention Definition	Number of Trials	Sample Size
Taylor et al (10)	2011	≤ 10% of participants with previous history of CVD	14	34,272
Brugts et al (8)	2009	≥ 80 of participants without established CVD	10	70,388
Mills et al (9)	2008	> 50% of participants had no history of CHD	20	65,261

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

Taylor et al (10) systematically reviewed RCTs to assess the harms and benefits of statins for primary prevention. Fourteen RCTs comparing statins with placebo were included and analyzed. Of these, 12 contributed data to the outcomes of interest; 10 contributed data on major coronary events and 7 on stroke (Table 2). The characteristics of these relevant studies are described in Appendix 3. Due to the large number of trials and time constraints of the rapid review method, the body of evidence was evaluated mainly according to the details on methodological quality assessment in the full Cochrane review. Original articles were consulted on an as-needed basis.

Table 2: Randomized Controlled Trials Contributing Outcome Data to Major Coronary Events and Stroke Events

Full Trial Name, Year	Acronym	Sample Size	Outcome Data	
			Major Coronary Events	Stroke Events
Asymptomatic Carotid Artery Progression Study, 1994 (11)	ACAPS	919	✓	✓
Kuopio Atherosclerosis Prevention Study, 1995 (12)	KAPS	447		✓
Carotid Atherosclerosis Italian Ultrasound Study, 1996 (13)	CAIUS	305	✓	
West of Scotland Coronary Prevention Study, 1997 (14)	WOSCOPS	6595	✓	✓
Air Force/Texas Coronary Atherosclerosis Prevention Study, 1998 (15)	AFCAPS/TexCAPS	6606	✓	
Collaborative Atorvastatin Diabetes Study, 2004 (16)	CARDS	2838	✓	✓
Prevention of Renal and Vascular Endstage Disease Intervention Trial, 2004 (17)	PREVEND IT	864		✓
Hypertension High Risk Management trial, 2005 (18)	HYRIM	87	✓	✓
Plaque Hypertension Lipid-Lowering Italian Study A, 2004 (19)	PHYLLIS A	253	✓	
Plaque Hypertension Lipid-Lowering Italian Study B , 2004 (cite) (19)	PHYLLIS B	255	✓	
Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, 2006 (20)	MEGA	8009	✓	✓
The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus, 2006 (21)	ASPEN	2410	✓	

Source: Taylor et al (10).

Major coronary events among individuals treated with statins were significantly reduced compared to placebo (Table 3). Stroke events were also significantly reduced among individuals treated with statins compared to placebo. Due to inadequate separate reporting and low rates of fatal and nonfatal coronary events in the trials, the composite measure of major coronary events is reported in the meta-analysis (i.e., fatal and nonfatal myocardial infarction and coronary deaths). The direction and magnitude of reduction in both major coronary events and stroke events was consistent across all 3 systematic reviews (Table 3).

Table 3: Effect Estimates for Effectiveness of Statins in Primary Prevention from Meta-Analyses

Author, Year	Major Coronary Events[a]		Stroke Events[b]	
	Number of Studies	Relative Risk (95% CI)	Number of Studies	Relative Risk (95% CI)
Taylor et al, 2011 (10)	10	0.72 (0.65–0.79)	7	0.78 (0.65–0.94)
Brugts et al, 2009 (8)	8	0.73[c] (0.63–0.85)	9	0.81[c] (0.71–0.93)
Mills et al, 2008[d] (9)	17	0.85 (0.77–0.95)	18	0.88 (0.78–1.00)

Abbreviations: CI, confidence intervals; RCT, randomized controlled trial.
[a]Includes nonfatal myocardial infarction and deaths from coronary disease.
[b]Includes fatal and nonfatal stroke events.
[c]Data presented as odds ratio, re-analyzed from article to obtain relative risk estimate using random effects model. Significant heterogeneity was found (I^2 = 63%, P = 0.01), which was accounted for by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial (ALLHAT-LLT). (22). The ALLHAT-LLT trial had the largest sample size of any single trial and running the analysis without it resolved the heterogeneity (I^2 = 32%, P = 0.19) but did not meaningfully change the effect estimate or significance (relative risk = 0.70, 95% CI, 0.61–0.79).
[d]Reports major CVD events, which includes coronary events.

Taylor and colleagues (10) planned subgroup analyses by gender, extent of hyperlipidemia, and age groups (i.e., older or younger than 65 years of age); however, they were not able to conduct them due to inadequate reporting of these data from included trials. Brugts et al (8) investigated the effects of statins overall as well as by predefined age, gender, and diabetic subgroups. As indicated in Table 3, the overall findings of effectiveness are consistent with the Taylor review (10), and there was no evidence of heterogeneity in treatment effect between subgroups. There was a significant reduction in major coronary events for both men and women, individuals older and younger than 65 years, and for individuals with and without diabetes mellitus. (8) For major cerebrovascular events (i.e., fatal and nonfatal strokes), there was a significant reduction in events only among individuals younger than 65 years of age, and nonsignificant trends toward a reduced number of events in all other groups. (8)

Mills et al (9) observed a reduction in major cardiovascular events in their review; however, there was significant heterogeneity between trials (I^2 = 61%, P = 0.001). The authors used meta-regression techniques to explain the heterogeneity, attributing it to the reporting of allocation concealment whereby those studies that reported appropriate allocation concealment had a marginally weaker therapeutic effect. (9) A reduction in all-stroke incidence was also found, although the effect did not reach statistical significance (P = 0.05). There was no evidence of significant heterogeneity for the stroke outcomes.

All 3 systematic reviews evaluated statin therapy for a minimum of 1 year and excluded cerivastatin, which was withdrawn from the market in 2001 due to serious adverse events. (23) The review by Taylor et al (10) focused on trials comparing statins with placebo, whereas the others included a wider array of comparators; Brugts et al (8) included studies comparing statins with placebo, usual care, or active control and Mills et al (9) included any RCT. Each of the systematic reviews reported the outcomes of interest in composite measures due to small numbers of events; however, Mills et al (9) reported "major cardiovascular disease" without explicating the definition. Of note, the systematic reviews differed considerably in the definition of primary prevention population, including trials with less than 10% of participants with a history of CVD up to nearly 50% of participants with a history of CVD (see Table 1). Despite these differences, there was general consistency in the effectiveness of statins in reducing major coronary events and strokes across the 3 systematic reviews.

Details of the quality assessment of the review by Taylor et al (10) are in Appendix 2.

Conclusions

- Three meta-analyses examining the effectiveness of statins for primary prevention were identified. Due to superior methodological quality and stringent criteria on exclusion of participants with a previous history of CVD, the meta-analysis by Taylor et al (10) was selected as the primary review to answer the research question, while the other 2 provided additional context.

- Statins significantly reduced the risk of major coronary events (i.e., combined fatal and nonfatal coronary events) in individuals without a previous history of CVD, compared to placebo. (GRADE quality of evidence: moderate)

- The risk of stroke (fatal and nonfatal) was significantly reduced in individuals without a previous history of CVD treated with statins, compared to placebo. (GRADE quality of evidence: low)

- The direction and magnitude of reduction in both major coronary events and stroke events was consistent across all 3 meta-analyses, despite differences in the definition of primary prevention populations.

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Appendices

Appendix 1: Literature Search Strategies

Search date: December 4, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD
Q: What is the effectiveness of statins for high cholesterol levels?
Limits: 2008-current; English
Filters: Meta-analyses; systematic reviews; Health Technology Assessments

Database: Ovid MEDLINE(R) 1946 to November Week 3 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 03, 2012, Embase 1980 to 2012 Week 48
Search Strategy:

#	Searches	Results
1	exp Dyslipidemias/ use mesz	60193
2	exp Lipids/ use mesz	875707
3	*Dyslipidemia/ use emez	6331
4	exp *Hyperlipidemia/ use emez	40933
5	*Abnormally High Substrate Concentration in Blood/ use emez	133
6	exp *Hyperlipoproteinemia/ use emez	4224
7	(hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?).ti,ab.	87872
8	(hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?).ti,ab.	51057
9	(((high* or elevat* or raise*) adj5 cholesterol*) or high- cholesterol* or highcholesterol*).ti,ab.	95755
10	lipid disorder?.ti.	735
11	or/1-10	1061048
12	exp *Anticholesteremic Agents/ use mesz	32392
13	exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ use mesz	17795
14	exp *Hypocholesterolemic Agent/ use emez	43610
15	(statin or statins).ti.	20089
16	(((hydroxymethylglutaryl-coa or hydroxymethylglutaryl-coenzyme a or hmg-coa) adj (reductase or inhibitor?)) or vastatin?).ti.	3692
17	Atorvastatin.mp.	27366
18	(Lipitor or liptonorm).ti.	119
19	Bervastatin.mp.	6
20	Cerivastatin.mp.	4031
21	(Baycol or Certa or Kazak or Lipobay or rivastatin).ti.	127
22	Compactin.mp.	1864
23	mevastatin.ti.	91
24	Crilvastatin.mp.	12
25	Dalvastatin.mp.	18
26	(Fluvastatin or Fluindostatin).mp.	8462
27	Glenvastatin.mp.	5
28	(Lovastatin or Mevinolin).mp.	18005
29	(mevacor or monacolin k).ti.	119
30	Mevinolinic Acid.mp.	55
31	(Monacolin J or Monacolin L or Monacolin M or Monacolin N or Monacolin X).mp.	87
32	Meglutol.mp.	125
33	Pitavastatin.mp.	1845
34	(itavastatin or nisvastatin).ti.	8
35	Pravastatin.mp.	19293

36	(pravacol or pravasin or lipemol or eptastatin or vasten or elisor or lipostat or bristacol or prareduct or apo-pravastatin or mevalotin or nu-pravastatin or selektine or pravachol or lin-pravastatin or liplat or vasten).ti.	53
37	Rosuvastatin.mp.	8784
38	Crestor.ti.	42
39	Simvastatin.mp.	32335
40	(synvinolin or Zocor).ti.	115
41	or/12-40	112772
42	11 and 41	42929
43	limit 42 to english language	36783
44	limit 43 to yr="2008 -Current"	12126
45	Meta Analysis.pt.	37949
46	Meta Analysis/ use emez	67461
47	Systematic Review/ use emez	55156
48	exp Technology Assessment, Biomedical/ use mesz	8944
49	Biomedical Technology Assessment/ use emez	11413
50	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	299862
51	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3991
52	or/45-51	360239
53	44 and 52	605
54	remove duplicates from 53	429

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Dyslipidemias] explode all trees	4517
#2	MeSH descriptor: [Lipids] explode all trees	30386
#3	(hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?):ti,ab,kw (Word variations have been searched)	1616
#4	(hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?):ti,ab,kw (Word variations have been searched)	5
#5	(((high* or elevat* or raise*) near/5 cholesterol*) or high- cholesterol* or highcholesterol*):ti,ab,kw (Word variations have been searched)	8754
#6	lipid disorder?:ti,ab,kw (Word variations have been searched)	399
#7	#1 or #2 or #3 or #4 or#5 or #6	31496
#8	MeSH descriptor: [Anticholesteremic Agents] explode all trees	3768
#9	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	2259
#10	statin or statins:ti (Word variations have been searched)	1004
#11	(((hydroxymethylglutaryl-coa or hydroxymethylglutaryl-coenzyme a or hmg-coa) near (reductase or inhibitor?)) or vastatin?):ti (Word variations have been searched)	213
#12	(Lipitor or liptonorm or Baycol or Certa or Kazak or Lipobay or rivastatin or mevastatin or mevacor or monacolin k or itavastatin or nisvastatin or pravacol or pravasin or lipemol or eptastatin or vasten or elisor or lipostat or bristacol or prareduct or apo-pravastatin or mevalotin or nu-pravastatin or selektine or pravachol or lin-pravastatin or liplat or vasten or Crestor or synvinolin or Zocor):ti (Word variations have been searched)	33
#13	(Atorvastatin or Bervastatin or Cerivastatin or Compactin or Crilvastatin or Dalvastatin or Fluvastatin or Fluindostatin or Glenvastatin or Lovastatin or Mevinolin or Mevinolinic Acid or Monacolin J or Monacolin L or Monacolin M or Monacolin N or Monacolin X or Meglutol or Pitavastatin or Pravastatin or Rosuvastatin or Simvastatin):ti,ab,kw (Word variations have been searched)	4782
#14	#8 or #9 or #10 or #11 or #12 or #13	6010
#15	#7 and #14 from 2008 to 2012	1075
#16	#15 in Trials	969
#17	#15 not #16	106

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR dyslipidemias EXPLODE ALL TREES	272
2	MeSH DESCRIPTOR lipids EXPLODE ALL TREES	1021
3	((hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?)):TI	40
4	((hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?)):TI	65
5	((((high* or elevat* or raise*) adj5 cholesterol*) or high- cholesterol* or highcholesterol*)):TI	5
6	(lipid disorder?):TI	0
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	1172
8	MeSH DESCRIPTOR Anticholesteremic Agents EXPLODE ALL TREES	421
9	MeSH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors EXPLODE ALL TREES	326
10	(statin or statins):TI	262
11	((((hydroxymethylglutaryl-coa or hydroxymethylglutaryl-coenzyme a or hmg-coa) near (reductase or inhibitor?)) or vastatin?)):TI	8
12	(Lipitor or liptonorm or Baycol or Certa or Kazak or Lipobay or rivastatin or mevastatin or mevacor or monacolin k or itavastatin or nisvastatin or pravacol or pravasin or lipemol or eptastatin or vasten or elisor or lipostat or bristacol or prareduct or apo-pravastatin or mevalotin or nu-pravastatin or selektine or pravachol or lin-pravastatin or liplat or vasten or Crestor or synvinolin or Zocor):TI	2
13	(Atorvastatin or Bervastatin or Cerivastatin or Compactin or Crilvastatin or Dalvastatin or Fluvastatin or Fluindostatin or Glenvastatin or Lovastatin or Mevinolin or Mevinolinic Acid or Monacolin J or Monacolin L or Monacolin M or Monacolin N or Monacolin X or Meglutol or Pitavastatin or Pravastatin or Rosuvastatin or Simvastatin):TI	101
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13	481
15	#7 AND #14	249
16	(#15):TI FROM 2008 TO 2012	97

Appendix 2: Quality Assessment Tables

Table A1: AMSTAR Scores of Systematic Reviews

Author, Year	AMSTAR Score[a]	1) Provided Study Design	2) Duplicate Study Selection	3) Broad Literature Search	4) Considered Status of Publication	5) Listed Studies	6) Provided Characteristics of Studies	7) Scientific Quality Assessed	8) Considered Quality in Report	9) Methods to Combine Appropriate	10) Assessed Publication Bias	11) Stated Conflict of Interest
Taylor et al, 2011 (10)	11	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Brugts et al, 2009 (8)	8	✓	✓	✓			✓	✓		✓	✓	✓
Mills et al, 2008 (9)	8	✓	✓	✓	✓		✓	✓		✓	✓	

[a]Maximum possible score is 11. Details of AMSTAR are described in Shea et al (24).

Table A2: GRADE Evidence Profile for Comparison of Statins and Control for Primary Prevention

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Major coronary events (nonfatal myocardial infarction and coronary deaths)							
10 (RCTs)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected[b]	None	⊕⊕⊕ Moderate
Stroke (fatal and nonfatal stroke events)							
7 (RCTs)	Serious limitations (-1)[c]	No serious limitations	No serious limitations	Serious limitations (-1)[d]	Undetected[b]	None	⊕⊕ Low

Abbreviations: CI, confidence interval; RCT, randomized controlled trial.

[a]5 studies did not provide detail on randomization method, and adequacy of allocation concealment was unclear in 7 studies. All but one study were double-blind and conducted intention-to-treat analysis, with one that was open-label statin treatment that utilized on-treatment analysis. (20) Two trials (15;16) were stopped early for benefit.

[b]All trials but 1 (14) received financial or instrumental support from the pharmaceutical industry; however, a funnel plot was used to assess publication bias and there was no evidence of asymmetry. The sample sizes of the included studies vary from small to large, and the studies represent significant and nonsignificant findings.

[c]Study randomization and allocation concealment method was unclear for 3 studies (14;20;21), respectively. Three studies performed on-treatment analysis for stroke outcomes (12;15;20) with one (12) reporting 17% of participants lost to follow up. One trial (16) was stopped early for benefit.

[d]The optimal information size (OIS) criterion was not met, and the event rates were very low (1.8% and 2.3% in the statin and control groups, respectively). Although the 95% CI around the summary estimate does not include 1.0, the CI's in 4 studies (11;12;17;21) cross this threshold.

Table A3: Risk of Bias Among Randomized Controlled Trials for the Comparison of Statins and Control for Primary Prevention

Trial, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
ACAPS, 1994 (11)	Limitations[a]	No limitations	No limitations	No limitations	No limitations
KAPS, 1995 (12)	No limitations	No limitations	Limitations[b]	No limitations	No limitations
CAIUS, 1996 (13)	No limitations	No limitations	No limitations	No limitations	No limitations
WOSCOPS, 1997 (14)	No limitations	No limitations	No limitations	No limitations	No limitations
AFCAPS/TexCAPS, 1998 (15)	Limitations[a]	No limitations	No limitations	No limitations	Limitations[c]
CARDS, 2004 (16)	No limitations	No limitations	No limitations	No limitations	Limitations[c]
PREVEND IT, 2004 (17)	No limitations	No limitations	Limitations[d]	No limitations	No limitations
HYRIM, 2005 (18)	Limitations[a]	No limitations	Limitations	No limitations	No limitations
PHYLLIS A, 2004 (19)	Limitations[a]	No limitations	No limitations	No limitations	No limitations
PHYLLIS B, 2004 (19)	Limitations[a]	No limitations	No limitations	No limitations	No limitations
MEGA, 2006 (20)	Limitations[a]	Limitations[e]	No Limitations	No limitations	No limitations
ASPEN, 2006 (21)	Limitations[a]	No limitations	No limitations	No limitations	No limitations

Abbreviations: ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASPEN, The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CAIUS, Carotid Atherosclerosis Italian Ultrasound Study; CARDS, Collaborative Atorvastatin Diabetes Study; HYRIM, Hypertension High Risk Management trial; KAPS, Kuopio Atherosclerosis Prevention Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PHYLLIS, Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; RCT, randomized controlled trial; WOSCOPS, West of Scotland Coronary Prevention Study.

[a]Method of random sequence generation and/or allocation concealment was not described.

[b]17% dropped out and were excluded from analysis.

[c]Trial was stopped early for benefit.

[d]Intention-to-treat analysis only for cardiovascular events, 6% lost to follow up.

[e]Open-label treatment with statins.

Source: Taylor et al., 2011 (10)

Appendix 3: Randomized Controlled Trials Included in Taylor Systematic Review

Table A4: Characteristics of Relevant Randomized Controlled Trials

Author, Year	N	Mean Age, years	Male, %	Intervention	Concomitant Treatment (as described)	Length of Follow Up, years
ACAPS, 1994 (11)	919	62	52.0	20 mg lovastatin + 1 mg warfarin	N/A	2.8
KAPS, 1995 (12)	447	57	100	4 mg pravastatin	N/A	3
CAIUS, 1996 (13)	305	55	53.0	40 mg pravastatin	N/A	3
WOSCOPS, 1997 (14)	6595	55	100	40 mg pravastatin	N/A	4.9
AFCAPS/TexCAPS, 1998 (15)	6606	58	57.5	20-40 mg lovastatin	Advice on diet	5.2
CARDS, 2004 (16)	2838	61.7	68.0	1 mg atorvastatin	Counselling on smoking cessation	3.9–4
PREVEND IT, 2004 (17)	864	51	64.5	40 mg pravastatin	N/A	3.8
HYRIM, 2005 (18)	87	57	100	40 mg fluvastatin	N/A	4
PHYLLIS A, 2004 (19)	253	58	40.7[a]	25 mg hydrochlorothiazide + 40 mg pravastatin	N/A	2.6
PHYLLIS B, 2004 (19)	255	58	40.0[a]	20 mg fosinopril + 40 mg pravastatin	N/A	2.6
MEGA, 2006 (20)	8009	59	32.0	10–20 mg pravastatin	Advice on diet	5
ASPEN, 2006 (21)	2410	60	62.5	10 mg atorvastatin	N/A	2.4

Abbreviations: ACAPS, Asyptomatic Caritid Artery Progression Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASPEN, The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CAIUS, Carotid Atherosclerosis Italian Ultrasound Study; CARDS, Collaborative Atorvastatin Diabetes Study; HYRIM, Hypertension High Risk Management trial ; KAPS, Kuopio Atherosclerosis Prevention Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PHYLLIS, Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; RCT, randomized controlled trial; WOSCOPS, West of Scotland Coronary Prevention Study.

[a]Estimated from treatment arm proportions provided in original article.

Source: Taylor et al., 2011 (10)

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