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Impact of conventional lipid-lowering therapy on circulating levels of PCSK9: protocol for a systematic review and meta-analysis of randomised controlled trials

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TW and LJ contributed equally.

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ABSTRACT

Introduction Conventional lipid-lowering agents, including statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid and Omega-3, are essential to the management of dyslipidaemia. However, these agents have been shown to increase the level of plasma proprotein convertase subtilisin/kexin 9 (PCSK9), a serine protease associated with increased cardiovascular risk. This review aims to investigate the impact of commonly available conventional lipid-lowering agents on circulating PCSK9 levels and lipid profiles.

Methods and analysis This protocol is conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. A systematic search will be conducted in the following databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of Science, SCOPUS and ScienceDirect. Additional information will be retrieved from clinical trial registries or from reference list searches. Published and peer-reviewed randomised controlled trials with adults receiving statin, ezetimibe, fibrate, bile acid sequestrant, nicotinic acid, bempedoic acid or Omega-3 monotherapy or in combination for at least 2 weeks, with availability of plasma PCSK9 at the beginning and end of treatment or the net changes in values, will be included. Study selection, data extraction and assessment of the risk of bias will be independently conducted by two investigators. Continuous data will be presented as a standardised mean difference with 95% confidence interval (CI) and dichotomous data as risk ratios with 95% CI. Subgroup analysis and sensitivity analysis will be performed when sufficient studies are included. Publication bias will be assessed with a funnel plot and Egger's test.

Ethics and dissemination Ethics approval is not required as this review will only include data from published sources. The results will be published in a peer-reviewed journal.

Patient and public involvement No patient or members of the general public are involved.

PROSPERO registration number CRD42022297942.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis will synthesise high-quality evidence from randomised controlled trials (RCTs) and quasi-RCTs.
⇒ Variation of the availability of agents among countries and regions is a potential source of bias and heterogeneity.
⇒ Variation of agents and doses among included studies will produce heterogeneity that complicates data synthesis and analysis.

INTRODUCTION

Lipid-lowering therapy is an essential part of the primary and secondary prevention of cardiovascular disease (CVD) in patients with dyslipidaemia, which is defined by the presence of hypercholesterolemia and/or hypertriglyceridemia.[1–3] The 2019 European Society of Cardiology and European Atherosclerosis Society guidelines recommended a treat-to-target approach with more intensive plasma low-density lipoprotein cholesterol (LDL-C) goals, which ranges from 3.0 mmol/L to 1.4 mmol/L for individuals of low to very high cardiovascular (CV) risk categories, respectively.[2] The guidelines recognised the need for a more comprehensive approach in the management of dyslipidaemia, involving both conventional lipid-lowering drugs, represented by statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid, omega-3 and novel agents represented by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase, inhibiting cholesterol production at the rate-limiting step.[4] Reduced hepatic cholesterol

synthesis leads to increased turnover of LDL receptors in hepatocytes and enhanced LDL clearance. Ezetimibe is a cholesterol absorption inhibitor that interacts with Niemann-Pick C1-like proteins 1 on the intestinal brush border. Ezetimibe further lowers plasma LDL-C by upregulating LDL receptors on the hepatocyte membrane, which is the hepatic response to lowered cholesterol uptake.[5] Fibrates are nuclear receptor peroxisome proliferator-activated receptor α agonists and can simulate triglyceride degradation, lower LDL-C levels and raise high-density lipoprotein cholesterol (HDL-C) levels in the bloodstream.[6] Bile acid sequestrants like cholestyramine and cholestipol bind to bile acids in the intestine and prevent their reabsorption.[7 8] Nicotinic acid reduces hepatic synthesis of very low-density lipoprotein particles and raises HDL-C levels in the blood.[9] Bempedoic acid is an adenosine triphosphate-citrate lyase inhibitor and can decrease cholesterol biosynthesis and increase LDL receptor expression.[10] Omega-3 polyunsaturated fatty acids from fish or plants have been suggested to improve blood fat composition and reduce the risk of CV mortality.[11] PCSK9 inhibitors are novel lipid-lowering agents that have been primarily approved for the treatment of individuals with inadequately controlled LDL-C with conventional lipid-lowing therapies.[2 12]

PCSK9 is a serine protease that binds to the LDL receptors on the cellular membrane of hepatocytes, inhibiting LDL receptor recycling and promoting its lysosomal degradation, which results in elevated plasma LDL-C as well as promotes vascular remodelling and atheroma development.[13] Accumulating evidence has demonstrated that elevated circulating PCSK9 level has been associated with increased CVD risk.[14] Although multiple randomised controlled trials (RCTs) and meta-analyses have demonstrated the efficacy of PCSK9 inhibitors in treating dyslipidaemia, several studies have reported that conventional lipid-lowering therapies could lead to increased circulating PCSK9 levels.[15–20] On the other hand, it has been reported that statin treatment raises PCSK9 in primarily the inactivated form.[21] Additionally, PCSK9 expression is controlled by the circadian rhythm and is influenced by multiple hormonal and nutritional factors, which further complicates the quantification of its plasma concentration.[22 23] Even though conventional lipid-lowering drugs are commonly used in clinical practice, it is rare to investigate the change in plasma PCSK9 levels when treating with these drugs. In light of this, it is necessary to further clarify the effect of conventional lipid-lowering drugs on the circulating activity of PCSK9.

Previous systematic reviews and meta-analyses have evaluated the effect of statins and fibrates on circulating PCSK9 levels.[24 25] However, the availability of recently published evidence, including several RCTs of high quality, underlines the need to reconduct those reviews.[19 26] Furthermore, previous reviews have not considered the effect of other commonly prescribed therapeutics, including ezetimibe, bile acid sequestrants, nicotinic acid, bempedoic acid and omega-3 on the level of circulating PCSK9. This systematic review and meta-analysis will identify the effects of commonly available conventional lipid-lowering drugs on circulating PSCK9 levels and lipid profiles in adults, to better understand the cause of PCSK9 changes and guide the clinical application of PCSK9 inhibitions when lipid-lowering therapy is combined with conventional drugs.

Box 1 Eligibility criteria of the systematic review and meta-analysis.

Inclusion criteria

1. Randomised controlled trials (RCTs) or quasi-RCTs (non-blinded or interrupted time series) with parallel or cross-over designs.
2. At least one kind of statin, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid or omega-3, is used in the intervention arm.
3. Treatment duration of at least 2 weeks.
4. Availability of plasma proprotein convertase subtilisin/kexin 9 (PCSK9) levels at the begin and end of treatment period, or the net changes in values.

Exclusion criteria

1. Studies not of RCT or quasi-RCT designs.
2. Studies that recruited subjects already receiving stable statin therapy.
3. Studies that did not provide mean (or median) plasma levels of PCSK9 at baseline and end of trial, or the net changes in values.

METHODS AND ANALYSIS

Registration

This protocol of systematic review and meta-analysis has been registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/). This protocol is in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (see online supplemental file 1, PRISMA-P checklist).[27] The completed systematic review and meta-analysis will be reported following the PRISMA guidelines.[28]

Study design

This systematic review and meta-analysis will consider published and peer-reviewed RCTs or quasi-RCTs of parallel or cross-over designs. Details of the eligibility criteria are listed in box 1. The study is expected to begin on 1 August 2022, and complete by 1 October 2022.

Participants

This systematic review and meta-analysis will include data from adults of at least 18 years of age, treated with any kind of statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid or omega-3 monotherapy or in combination for at least 2 weeks, in isolation or in comparison with placebo, diet, no intervention or another type of lipid-lowering therapy.

Outcomes

The primary outcome is the mean difference in plasma PCSK9 levels. The secondary outcomes are the differences in lipid profile between baseline and the completion of

the lipid-lowing intervention. The lipid profiles include total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein A1, apolipoprotein B and lipoprotein[a].

Search strategy

Relevant studies will be identified through a systematic search in online databases, using search strategies developed with the assistance of information specialists. Electronic bibliographic databases, including MEDLINE, CENTRAL, EMBASE, Web of Science (Science and Social Science Citation Index), SCOPUS and ScienceDirect will be searched. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched for relevant RCTs. Further information will be retrieved from published sources by accessing the grey literature sources or contacting the original authors when necessary. The reference lists of related review and articles will be reviewed to identify trials missed during the searches. Additionally, we also will search the grey databases such as preprinted database for unpublished literature. A filter designed for retrieval of RCTs with maximised sensitivity will be applied.[29] The search will be limited to studies published from 1 January 2003, to the formal search date. The search strategy for MEDLINE (Ovid) is presented in online supplemental file 2. Search strategies for other databases will be adapted accordingly. The searches will be rerun just before the final analyses and further studies retrieved for inclusion. Reference lists and citations of identified trials will be further examined for inclusion.

Study selection and data extraction

The primary selection of potentially eligible studies will be conducted independently by two authors (JL and TH) by reviewing the titles and abstracts of publications identified in the electronic searches. The same two authors will independently assess the full manuscripts (if available) against the eligibility criteria, and, where necessary, resolve any disagreement with discussion or the involvement of the third author (TW).

Primary and secondary outcome data will be independently extracted by the same two authors. Apart from the primary and secondary outcomes, further information intended to be extracted includes (1) general information: title, journal, authors, country or region, year of publication, (2) trial characteristics: study design, target condition, duration of follow-up, allocation concealment and method, randomisation and method, blinding (outcome assessors), checking of blinding, intention-to-treat analysis, (3) intervention: loading dose, dosage, duration of treatment, (4) participants: total number and number in comparison, age, gender, diet, hormone levels, time of blood sample collection, the similarity of groups at baseline, withdrawals/losses to follow-up or any other related demographic or clinical information. Disagreement will be resolved either by discussion or by the involvement of the third investigator (TW). If necessary, the authors of the included studies will be contacted via email for the key missing data.

Quality assessment

Two authors (XZ and XW) will independently assess the risk of bias, with any disagreement resolved either by discussion or by the involvement of the third author (TW). The risk of bias of individual RCTs will be assessed using the Cochrane Risk of Bias V.2.0 assessment tool, and the individual items will be graded as of 'low', 'unclear' or 'high' risk of bias.[30] The items include: (1) random sequence generation, (2) allocation concealment, (3) intervention blinding, (4) outcome blinding, (5) missing outcome data, (6) selective reporting, (7) other biases.

Data synthesis and analysis

Data management and synthesis

We will use EndNote X V.9 software to manage the literature and Microsoft Excel to synthesise the extracted data. RevMan V.5.4 will be used for data integration.[31] Continuous data will be presented as standardised mean difference with 95% CI, and dichotomous data will be presented as risk ratios with 95% CI.

Assessment of heterogeneity

For trials with statistically significant heterogeneity (p value <0.1), a random-effects model will be applied to calculate the pooled estimates of the treatment effect. If a significant level of heterogeneity is not identified, the pooled estimates of the treatment effect for each outcome will be calculated with Mantel-Haenszel fixed-effect model. The findings will be presented as forest plots. Clinical heterogeneity will be assessed by examining differences in study designs, participant characteristics, the direction of treatment effect and overlap of CI on forest plots. Statistical heterogeneity among studies will be calculated using the I^2 statistic and τ^2, the latter calculated from random-effects model. The results will be classified as mild (<40%), moderate (40–60%) or substantial (>60%) heterogeneity. Where substantial heterogeneity is present between studies, subgroup and sensitivity analyses will be performed to further identify potential sources of heterogeneity. If substantial heterogeneity persists after these analyses, the narrative review will be performed.

Subgroup analysis

Subgroup analysis is planned when a sufficient number of studies can be included and such analysis is deemed appropriate by heterogeneity analysis. Meta-regression will be conducted to explore whether treatment effects differ between study baseline characteristics on a continuous scale. Subgroup analysis will be planned based on the following items: gender, age, ethnicity, types of lipid-lowering therapy, monotherapy or combined therapy, dose, duration of treatment and the measurement methods of PCSK9.

Sensitivity analysis

Sensitivity analysis will be used to assess the validity and robustness of the review's findings by excluding studies with a high risk of bias in one or more domains and

comparing the direction and magnitude of results of the sensitivity analysis to that of the primary analysis.

Assessment of reporting biases

If equal or more than 10 studies can be included in the systematic review, funnel plot analysis and Egger's test will be performed to assess whether this review is subjected to publication bias.[32]

Grading the quality of evidence

The quality of evidence for outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation system. Evidence will be examined based on criteria of study design, risk of bias, imprecision, inconsistency, indirectness and magnitude of effect.[33]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research. Patient consent for publication is not required.

DISCUSSION

The current systematic review and meta-analysis will assess the effect of the conventional lipid-lowing agents such as statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid and omega-3 on plasma PCSK9 levels. Plasma PCSK9, binding to LDL receptors on hepatic cell membranes, can prevent LDL receptors from recycling to the cellular surface and increase its lysosomal degradation.[34] LDL-C absorption is highly reliant on the LDL receptor level. Elevated plasma PCSK9 levels will impair the lowing-lipid effect of conventional agents.[35 36] Therefore, it is necessary to determine the effect of conventional lipid-lowing agents on plasma PCSK9 levels for the management of dyslipidaemia and atherosclerotic CVDs.

This systematic review and meta-analysis has some limitations. First, some agents, for instance, nicotinic acid, are not globally available. This variation in availability may be a potential source of bias and heterogeneity. In addition, differences in agents and doses between studies could add to the heterogeneity of the analysis. However, subgroup and sensitivity analyses will be used when appropriate to explore the sources of heterogeneity and the effects of heterogeneity on the results. Furthermore, the current study will only include RCTs and quasi-RCTs with high-quality evidence, improving the reliability of the review's findings and providing a solid conclusion for the assessment of the effect of conventional lipid-lowing agents on plasma PCSK9 levels.

Ethics and dissemination

Ethics approval is not required for this study as only published information will be included. Findings of this systematic review and meta-analysis will be published in a peer-reviewed journal after completion.

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Contributors LJ and TW contributed to the conception of the study. The systematic review protocol was drafted by TH and was reviewed by JL and TW. The search strategy was developed by RX and XW and will be performed by YY, LL and XZ. YZ, YJ, JW and HY will independently screen the potential studies, extract data from the included studies, assess the risk of bias, and complete the data synthesis. YM and BY will arbitrate in cases of disagreement and ensure the absence of errors. All authors reviewed and approved the publication of the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable, as no datasets are generated for this protocol.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location (Page/Line)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1/line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P7/line 143
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1-2/lines 4-26, emails in online submission system
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P15/lines 274-280
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	not applicable
Support:			P15/lines 281-283
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P7/lines 129-134
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P7/lines 134-138
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P8/lines 150-152, Table 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P10/lines 165-180
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary_File_2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P12/lines 208-211
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P11/lines 182-186
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P11/lines 186-197
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P11/lines 186-197
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P10/lines 160-163
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P12/lines 199-205
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P13/lines 220-224
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P12/lines 213-219
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P13/lines 226-235
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P13/lines 223-224
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P13/lines 237-239
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P14/lines 241-244

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Precis: This systematic review and meta-analysis synthesize high-quality evidence from RCTs and quasi-RCTs to investigate the impact of commonly available conventional lipid-lowering agents on circulating levels of PCSK9 and lipid profiles.

Primary search strategy on MEDLINE

#1	Exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
#2	(statin$ OR atorvastatin OR fluvastatin OR lovastatin or pitavastatin or pravastatin or cerivastatin OR rosuvastatin or simvastatin).tw. OR (lipitor$ OR baycol OR lescol OR mevacor OR altocor OR pravachol OR lipostat OR crestor OR zocor OR mevinolin OR compactin OR fluindostatin).tw.
#3	#1 OR #2
#4	Exp Fibric Acids/
#5	(fibric acid OR fibrate$).tw. OR (gemfibrozil OR bezafibrate OR ciprofibrat$ OR fenofibrate OR clofibrate OR asufibrat$ OR befibrat$ OR befizal OR bezacur OR bezafibratum OR bezafisal OR dezagen OR bezalande OR bezalex OR bezapuren OR bezastad OR bionolip OR cedur OR closer OR difaterol OR durabezur OR eulitop OR hadiel OR klestran OR liparol OR lipitrol OR lipocin OR lipox OR norlip OR polyzalip OR redalip OR sklerofibrate OR regadrin OR befizal OR bezamerck OR reducterol OR bezalip OR solibay OR cedur OR azufibrate OR difaterol OR lipox OR clofenapate OR clofibric acid OR clofibrinic acid OR livesan OR liparison OR durafenat OR supralip OR lofibra OR fenobeta OR lipantil OR tricor OR controlip OR gemfibrozil OR gemfibro$ OR lipazil OR lopid OR nugemfibrozil OR apogemfibrozil).tw.
#6	#4 OR #5
#7	(Exp Ezetimibe/) OR (ezetimibe OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy).tw.
#8	(Cholestyramine OR nicotinic acid OR colestipol OR (Cholesterol next lowering) OR (lipid next lowering)).tw.
#9	(Bempedoic$ or Nexletol or Nexlizet or Nilemdo$ or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).tw.
#10	(exp Fish Oils/) OR (exp Fatty Acids, Omega-3/) OR (omega-3 or omega3 or (omega adj5 fat)).tw. OR (eicosapentaen or docosahexaen or linseed oil or linolenic acids or PUFA or n-3PUFA or n3PUFA or perilla or linseed or maxepa or perilla or linseed or maxepa or dha or docosahex$ or eicosapent4 or epa or ethyl$eicosapent or ethyleicosapent).tw. OR (n3 or n$3 or w3 or w$3) adj3 polyunsaturat$).tw. OR (n3 or n$3 or w3 or w$3) adj3 oil).tw. OR (fish adj2 oil).tw.OR (cod adj2 oil).tw.
#11	#7 OR #8 OR #9 OR #10
#12	#3 OR #6 OR #11
#13	Exp Proprotein Convertase 9/
#14	(PCSK9 OR PCSK 9 OR PCSK$9 OR Proprotein convertase subtilisin kexin type 9 OR Proprotein convertase subtilisin$kexin type 9 OR proprotein convertase$ OR pro$protein convertase$ OR NARC1 OR NARC 1 OR NARC$1 OR neuronal

	apoptosis regulated convertase1 OR neuronal apoptosis regulated convertase 1 OR neuronal apoptosis regulated convertase$1).tw.
#15	#11 OR #12
#16	#10 AND #13
#17	Randomized controlled trial.pt.
#18	Controlled clinical trial.pt.
#19	Randomized.ab.
#20	Placebo.ab.
#21	Drug therapy.fs.
#22	Randomly.ab.
#23	Trial.ab.
#24	Groups.ab.
#25	#15 OR #16 OR #17 OR #18 OR #19 OR #20 #21 OR #22
#26	#14 AND #23

Formal search strategy

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations

No.	Searches
1	Proprotein Convertase 9/
2	(PCSK9 or PCSK-9).tw.
3	((kexin$ adj3 "9") or (subtilisin$ adj5 "9")).tw.
4	((proprotein or pro-protein) adj3 convertase$ adj5 "9").tw.
5	(NARC1 or NARC-1).tw.
6	((neur$ or apopt$) adj5 convertase$ adj3 "1").tw.
7	**1 or 2 or 3 or 4 or 5 or 6**
8	Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Hydroxymethylglutaryl CoA Reductases/
9	((("hydroxymethylglutaryl Coenzyme" or "hydroxymethylglutaryl CoA" or "HMG CoA") adj5 inhib$) or statin or statins).tw.
10	(anticholesterol?emic or hypocholesterol?emic or hypocholester?emic or anticholester?emic).tw.
11	((cholesterol or lipid$ or LDL or HDL or TG or TC or triglyceride) adj3 (reduc$ or lower$ or inhib$ or drug$ or agent$)).tw.
12	Atorvastatin/ or exp Simvastatin/ or exp Lovastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/

13	(Atorvastatin or atorlip or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).tw.
14	(Simvastatin or Synvinolin or "MK 733" or MK733 or Zocor or avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethicol or eucor or ifistatin or kavelor or klonastin or kolestevan or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or "nor vastina" or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or sinvastatin or sinvinolin or sivastin or starzoco or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or zocord or zovast or inegy or vytorin or zetsim or zintrepid or cholib or fenofibrate$ or "niacin simvastatin" or simcor or "rosiglitazone simvastatin" or avandastat or "sitagliptin simvastatin" or sitagliptin phosphate$ or juvisync).tw.
15	(Pitavastatin or nisvastatin or itavastatin or alipza or livalo or livazo or pitava or ribar or vezepra or "P 872441" or "NK 104" or "nk104" or "nks 104" or nks104 or lippiza or nikita or trolise or zypitamag).tw.
16	(Cerivastatin or kazak or rivastatin or certa or "bay w 6228" or "bay w6228" or baycol or lipobay).tw
17	(Lovastatin or mevinolin or monacolin or "6 Methylcompactin" or "MK 803" or MK803 or mk0803 or mevacor or altocor or altoprev or artein or belvas or birotin or cholestra or cysin or ellanco or elstatin or lipdip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or meverstin or mevinacor or monakolin or "msd 803" or neolipid or nergadan or ovasta or rodatin or rovacor or taucor or advicor).tw.
18	(Fluvastatin or fluindostatin or lescol or "XU 62-320" or "XU 62320" or xu62320 or canef or cranoc or "fractal lp" or leucol or lochol or locol or "sri 62320" or sri62320 or vastin).tw.
19	(Pravastatin or eptastatin or vasten or "CS 514" or CS514 or lipemol or liplat or "nu pravastatin" or prareduct or mevalotin or pravachol or elisor or selektine or pravacol or pravasin or lipostat or "RMS 431" or RMS431 or "SQ 31000" or SQ31000 or "SQ 31,000" or SQ31,000 or bristacol or astin or cholespar or epatostantin or eptastatine or kenstatin or lipidal or liprevil or novales or prascolend or prastan or prava or pravaselect or pravasine or pravator or pravyl or sanaprav or selipran or stanidine or vasopran or xipral or pravafenix).tw.
20	(Rosuvastatin or ZD4522 or "ZD 4522" or crestor or rosuvas or "s 4522" or s4522 or certriad).tw.
21	**8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20**

22	exp Ezetimibe/
23	(ezetimibe or ezetimib or ezetrol or zetia or vytorin or inegy or "SCH 58235" or SCH58235).tw.
24	**22 or 23**
25	exp Fibric Acids/
26	(fibric acid or fibrate$ or gemfibrozil or bezafibrate or ciprofibrat$ or fenofibrate or clofibrate or asufibrat$ or befibrat$ or befizal or bezacur or bezafibratum or bezafisal or dezagen or bezalande or bezalex or bezapuren or bezastad or bionolip or cedur or closer or difaterol or durabezur or eulitop or hadiel or klestran or liparol or lipitrol or lipocin or lipox or norlip or polyzalip or redalip or sklerofibrate or regadrin or befizal or bezamerck or reducterol or bezalip or solibay or cedur or azufibrate or difaterol or lipox or clofenapate or clofibric acid or clofibrinic acid or livesan or liparison or durafenat or supralip or lofibra or fenobeta or lipantil or tricor or controlip or gemfibrozil or gemfibro$ or lipazil or lopid or nugemfibrozil or apogemfibrozil).tw.
27	**25 or 26**
28	exp Nicotinic Acids/
29	(niacin or nicotinic acid or nicamin or nicotinate or "nico 400" or nico-400 or nico400 or induracin or nicolar or nicocap or wampocap or nicobid or "3 pyridinecarboxylic acid" or 3-pyridinecarboxylic acid or enduracin or niacinamide or papulex or "vitamin b3" or "vitamin b 3" or vitamin pp or nicotinamide or enduramide or nicobion or "3 pyridinecarboxamide" or 3-pyridinecarboxamide or nicotinsaureamid or Niaspan or Tredaptive or antipellagra factor or niacor or nicotinex or vitb3 or nicamid or nicomide-t or nicosedine).tw.
30	**28 or 29**
31	exp "Bile Acids and Salts"/ and (sequestering agents/ or chelating agents/)
32	((((bile adj3 acid$) or BA) adj3 sequestrant$) or BAS).tw.
33	Colesevelam Hydrochloride/ or Cholestyramine Resin/ or Colestipol/
34	(Colesevelam or Cholestagel or Welchol or Lodalis or "GT 31104" or GT-31104 or GT31-104 or "GT31 104" or GT31104).tw.
35	(Cholestyramine$ or Colestyramin$ or Questran$ or Prevalite or Cuemid$ or Quantalan$ or MK-135 or MK135 or "MK 135").tw.
36	(Colestipol or Colestid or Cholestabyl or "U-26597 A" or "U 26597 A" or "U26597 A" or Colestimide or colestilan or MCI-196).tw.
37	**31 or 32 or 33 or 34 or 35 or 36**

38	((bempedoi$ adj3 acid$) or Nexletol or Nexlizet or Nilemdo or Nustendi or Bempedoate or "ETC 1002" or ETC1002 or ETC-1002 or ESP55016 or ESP-55016 or "ESP 55016" or 738606-46-7).tw.
39	exp Fatty Acids, Omega-3/ or Fish Oils/ or Cod Liver Oil/
40	(omega3$ or "omega 3$" or fatty acid$ or PUFA or n-3PUFA$ or n3PUFA$ or dha or docosahex$ or eicosapent$ or epa or ethyl-eicosapent$ or ethyleicosapent$ or alphalinolen$ or alpha-linolen$ or linolenate$ or linolenic$).tw.
41	((n3 or n-3 or w3 or w-3) adj3 (oil$ or polyunsaturat$)).tw.
42	((fish$ or cod) adj2 oil$).tw.
43	**39 or 40 or 41 or 42**
44	**21 or 24 or 27 or 30 or 37 or 38 or 43**
45	randomized controlled trial.pt.
46	controlled clinical trial.pt.
47	randomized.ab.
48	placebo.ab.
49	randomly.ab.
50	trial.ab.
51	groups.ab.
52	drug therapy.fs.
53	**45 or 46 or 47 or 48 or 49 or 50 or 51 or 52**
54	**7 and 44 and 53**
55	exp animals/ not humans.sh.
56	54 not 55
57	limit 56 to (english language and yr="2003 -Current")

Cochrane Central Register of Controlled Trials (CENTRAL)

No.	Searches
#1	MeSH descriptor: [Proprotein Convertase 9] this term only
#2	PCSK9 or PCSK-9
#3	(kexin* OR subtilisin*) AND 9
#4	(proprotein OR pro-protein) AND convertase* AND 9
#5	NARC1 OR NARC-1
#6	(neur* or apopt*) AND convertase* AND 1
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only
#9	MeSH descriptor: [Hydroxymethylglutaryl CoA Reductases] explode all trees
#10	(("hydroxymethylglutaryl Coenzyme" OR "hydroxymethylglutaryl CoA" OR "HMG CoA") AND inhib*) OR statin OR statins
#11	anticholesterol?emic OR hypocholesterol?emic OR hypocholester?emic OR anticholester?emic
#12	(cholesterol OR lipid* OR LDL OR HDL OR TG OR TC OR triglyceride) AND (reduc* OR lower* OR inhib* OR drug* OR agent*)
#13	MeSH descriptor: [Atorvastatin] this term only
#14	MeSH descriptor: [Simvastatin] explode all trees
#15	MeSH descriptor: [Lovastatin] explode all trees
#16	MeSH descriptor: [Fluvastatin] this term only
#17	MeSH descriptor: [Pravastatin] this term only
#18	MeSH descriptor: [Rosuvastatin Calcium] this term only
#19	Atorvastatin OR atorlip OR atovarol OR cardyl OR "ci 981" OR ci981 OR glustar OR lipibec OR lipitor OR liprimar OR liptonorm OR lowlipen OR sortis OR storvas OR tahor OR torvast OR totalip OR xarator OR "ym 548" OR ym548 OR zarator
#20	Simvastatin OR Synvinolin OR "MK 733" OR MK733 OR Zocor OR avastinee OR cholestat OR clinfar OR colastatina OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR kavelor OR klonastin OR kolestevan OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR "nor vastina" OR normofat OR orovas OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simvacor OR simvahex OR simvalord OR simvastar OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR

	starzoco OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocord OR zovast OR inegy OR vytorin OR zetsim OR zintrepid OR cholib OR fenofibrate* OR "niacin simvastatin" OR simcor OR "rosiglitazone simvastatin" OR avandastat OR "sitagliptin simvastatin" OR sitagliptin phosphate* OR juvisync
#21	Pitavastatin OR nisvastatin OR itavastatin OR alipza OR livalo OR livazo OR pitava OR ribar OR vezepra OR "P 872441" OR "NK 104" OR "nk104" OR "nks 104" OR nks104 OR lippiza OR nikita OR trolise OR zypitamag
#22	Cerivastatin OR kazak OR rivastatin OR certa OR "bay w 6228" OR "bay w6228" OR baycol OR lipobay
#23	Lovastatin OR mevinolin OR monacolin OR "6 Methylcompactin" OR "MK 803" OR MK803 OR mk0803 OR mevacor OR altocor OR altoprev OR artein OR belvas OR birotin OR cholestra OR cysin OR ellanco OR elstatin OR lipdip OR lipivas OR lofacol OR lomar OR lostatin OR lovacel OR lovacol OR lovalip OR lovalord OR lovastan OR lovasterol OR lovastin OR lovatadin OR lowachol OR lozutin OR medostatin OR meverstin OR mevinacor OR monakolin OR "msd 803" OR neolipid OR nergadan OR ovasta OR rodatin OR rovacor OR taucor OR advicor
#24	Fluvastatin OR fluindostatin OR lescol OR "XU 62-320" OR "XU 62320" OR xu62320 OR canef OR cranoc OR "fractal lp" OR leucol OR lochol OR locol OR "sri 62320" OR sri62320 OR vastin
#25	Pravastatin OR eptastatin OR vasten OR "CS 514" OR CS514 OR lipemol OR liplat OR "nu pravastatin" OR prareduct OR mevalotin OR pravachol OR elisor OR selektine OR pravacol OR pravasin OR lipostat OR "RMS 431" OR RMS431 OR "SQ 31000" OR SQ31000 OR "SQ 31,000" OR SQ31,000 OR bristacol OR astin OR cholespar OR epatostantin OR eptastatine OR kenstatin OR lipidal OR liprevil OR novales OR prascolend OR prastan OR prava OR pravaselect OR pravasine OR pravator OR pravyl OR sanaprav OR selipran OR stanidine OR vasopran OR xipral OR pravafenix
#26	Rosuvastatin OR ZD4522 OR "ZD 4522" OR crestor OR rosuvas OR "s 4522" OR s4522 OR certriad
#27	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR 23 OR #24 OR #25 OR #26
#28	MeSH descriptor: [Ezetimibe] explode all trees
#29	ezetimibe OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy OR "SCH 58235" OR SCH58235
#30	#28 OR #29
#31	MeSH descriptor: [Fibric Acids] explode all trees

#32	fibric acid OR fibrate* OR gemfibrozil OR bezafibrate OR ciprofibrat* OR fenofibrate OR clofibrate OR asufibrat* OR befibrat* OR befizal OR bezacur OR bezafibratum OR bezafisal OR dezagen OR bezalande OR bezalex OR bezapuren OR bezastad OR bionolip OR cedur OR closer OR difaterol OR durabezur OR eulitop OR hadiel OR klestran OR liparol OR lipitrol OR lipocin OR lipox OR norlip OR polyzalip OR redalip OR sklerofibrate OR regadrin OR befizal OR bezamerck OR reducterol OR bezalip OR solibay OR cedur OR azufibrate OR difaterol OR lipox OR clofenapate OR clofibric acid OR clofibrinic acid OR livesan OR liparison OR durafenat OR supralip OR lofibra OR fenobeta OR lipantil OR tricor OR controlip OR gemfibrozil OR gemfibro* OR lipazil OR lopid OR nugemfibrozil OR apogemfibrozil
#33	#31 OR #32
#34	MeSH descriptor: [Nicotinic Acids] in all MeSH products
#35	niacin OR nicotinic acid OR nicamin OR nicotinate OR "nico 400" OR nico-400 OR nico400 OR induracin OR nicolar OR nicocap OR wampocap OR nicobid OR "3 pyridinecarboxylic acid" OR enduracin OR niacinamide OR papulex OR "vitamin b3" OR "vitamin b 3" OR vitamin pp OR nicotinamide OR enduramide OR nicobion OR "3 pyridinecarboxamide" OR nicotinsaureamid OR Niaspan OR Tredaptive OR antipellagra factor OR niacor OR nicotinex OR vitb3 OR nicamid OR nicomide-t OR nicosedine
#36	#34 OR #35
#37	MeSH descriptor: [Bile Acids and Salts] explode all trees
#38	MeSH descriptor: [Sequestering Agents] this term only
#39	MeSH descriptor: [Chelating Agents] this term only
#40	(#38 OR #39) AND #37
#41	(((bile AND acid*) OR BA) AND sequestrant*) OR BAS
#42	MeSH descriptor: [Colesevelam Hydrochloride] this term only
#43	MeSH descriptor: [Cholestyramine Resin] this term only
#44	MeSH descriptor: [Colestipol] this term only
#45	Colesevelam OR Cholestagel OR Welchol OR Lodalis OR "GT 31104" OR GT-31104 OR "GT31 104" OR GT31104
#46	Cholestyramine* OR Colestyramin* OR Questran* OR Prevalite OR Cuemid* OR Quantalan* OR MK-135 OR MK135 OR "MK 135"
#47	Colestipol OR Colestid OR Cholestabyl OR "U-26597 A" OR "U 26597 A" OR "U26597 A" OR Colestimide OR colestilan OR MCI-196
#48	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47

#49	bempedoi* AND acid* or Nexletol or Nexlizet or Nilemdo or Nustendi or Bempedoate or "ETC 1002" or ETC1002 or ETC-1002 or ESP55016 or ESP-55016 or "ESP 55016" or "738606 46 7"
#50	MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
#51	MeSH descriptor: [Fish Oils] this term only
#52	MeSH descriptor: [Cod Liver Oil] this term only
#53	omega3* or "omega 3*" or fatty acid* or PUFA or n-3PUFA* or n3PUFA* or dha or docosahex* or eicosapent* or epa or ethyl-eicosapent* or ethyleicosapent* or alphalinolen* or alpha-linolen* or linolenate* or linolenic*
#54	(n3 or n-3 or w3 or w-3) AND (oil* or polyunsaturat*)
#55	(fish* or cod) AND oil*
#56	#50 OR #51 OR #52 OR #53 OR #54 OR #55
#57	#27 OR #30 OR #33 OR #36 OR #48 OR #49 OR #56
#58	#7 AND #57 with Publication Year from 2003 to present , in Trials

Embase

No.	Searches
#1	'proprotein convertase 9'/de
#2	pcsk9 OR 'pcsk 9' OR (kexin* NEAR/3 '9') OR (subtilisin* NEAR/5 '9') OR ((proprotein OR 'pro protein') NEAR/3 convertase* NEAR/5 '9') OR ((neur* OR apopt*) NEAR/5 convertase* NEAR/3 '1') OR narc1 OR 'narc 1'
#3	#1 OR #2
#4	'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR 'hydroxymethylglutaryl coenzyme a reductase'/de OR 'atorvastatin'/de OR 'simvastatin'/de OR 'lovastatin plus nicotinic acid'/de OR 'pravastatin'/de OR 'rosuvastatin'/de
#5	(('hydroxymethylglutaryl coenzyme' OR 'hydroxymethylglutaryl coa' OR 'hmg coa') NEAR/5 inhib*) OR statin OR statins OR anticholesterol$emic OR hypocholesterol$emic OR hypocholester$emic OR anticholester$emic OR ((cholesterol OR lipid* OR ldl OR hdl OR tg OR tc OR triglyceride) NEAR/3 (reduc* OR lower* OR inhib* OR drug* OR agent*))
#6	atorvastatin OR atorlip OR atovarol OR cardyl OR 'ci 981' OR ci981 OR glustar OR lipibec OR lipitor OR liprimar OR liptonorm OR lowlipen OR sortis OR storvas OR tahor OR torvast OR totalip OR xarator OR 'ym 548' OR ym548 OR zarator
#7	simvastatin OR synvinolin OR 'mk 733' OR mk733 OR zocor OR avastinee OR cholestat OR clinfar OR colastatina OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR kavelor OR klonastin OR kolestevan OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR 'nor vastina' OR normofat OR orovas OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simvacor OR simvahex OR simvalord OR simvastar OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR starzoco OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocord OR zovast OR inegy OR vytorin OR zetsim OR zintrepid OR cholib OR fenofibrate* OR 'niacin simvastatin' OR simcor OR 'rosiglitazone simvastatin' OR avandastat OR 'sitagliptin simvastatin' OR 'sitagliptin phosphate*' OR juvisync
#8	pitavastatin OR nisvastatin OR itavastatin OR alipza OR livalo OR livazo OR pitava OR ribar OR vezepra OR 'p 872441' OR 'nk 104' OR 'nk104' OR 'nks 104' OR nks104 OR lippiza OR nikita OR trolise OR zypitamag
#9	cerivastatin OR kazak OR rivastatin OR certa OR 'bay w 6228' OR 'bay w6228' OR baycol OR lipobay
#10	lovastatin OR mevinolin OR monacolin OR '6 methylcompactin' OR 'mk 803' OR mk803 OR mk0803 OR mevacor OR altocor OR altoprev OR artein OR belvas OR birotin OR cholestra OR cysin OR ellanco OR elstatin OR lipdip OR lipivas OR lofacol OR lomar OR

	lostatin OR lovacel OR lovacol OR lovalip OR lovalord OR lovastan OR lovasterol OR lovastin OR lovatadin OR lowachol OR lozutin OR medostatin OR meverstin OR mevinacor OR monakolin OR 'msd 803' OR neolipid OR nergadan OR ovasta OR rodatin OR rovacor OR taucor OR advicor
#11	fluvastatin OR fluindostatin OR lescol OR 'xu 62-320' OR 'xu 62320' OR xu62320 OR canef OR cranoc OR 'fractal lp' OR leucol OR lochol OR locol OR 'sri 62320' OR sri62320 OR vastin
#12	pravastatin OR eptastatin OR vasten OR 'cs 514' OR cs514 OR lipemol OR liplat OR 'nu pravastatin' OR prareduct OR mevalotin OR pravachol OR elisor OR selektine OR pravacol OR pravasin OR lipostat OR 'rms 431' OR rms431 OR 'sq 31000' OR sq31000 OR 'sq 31,000' OR sq31,000 OR bristacol OR astin OR cholespar OR epatostantin OR eptastatine OR kenstatin OR lipidal OR liprevil OR novales OR prascolend OR prastan OR prava OR pravaselect OR pravasine OR pravator OR pravyl OR sanaprav OR selipran OR stanidine OR vasopran OR xipral OR pravafenix
#13	rosuvastatin OR zd4522 OR 'zd 4522' OR crestor OR rosuvas OR 's 4522' OR s4522 OR certriad
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	'ezetimibe'/de OR ezetimibe OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy OR 'sch 58235' OR sch58235
#16	'fibric acid derivative'/exp OR 'fibric acid' OR fibrate* OR bezafibrate OR ciprofibrat* OR fenofibrate OR clofibrate OR asufibrat* OR befibrat* OR bezacur OR bezafibratum OR bezafisal OR dezagen OR bezalande OR bezalex OR bezapuren OR bezastad OR bionolip OR closer OR durabezur OR eulitop OR hadiel OR klestran OR liparol OR lipitrol OR lipocin OR norlip OR polyzalip OR redalip OR sklerofibrate OR regadrin OR befizal OR bezamerck OR reducterol OR bezalip OR solibay OR cedur OR azufibrate OR difaterol OR lipox OR clofenapate OR 'clofibric acid' OR 'clofibrinic acid' OR livesan OR liparison OR durafenat OR supralip OR lofibra OR fenobeta OR lipantil OR tricor OR controlip OR gemfibrozil OR gemfibro* OR lipazil OR lopid OR nugemfibrozil OR apogemfibrozil
#17	'nicotinic acid'/de OR niacin OR 'nicotinic acid' OR nicamin OR nicotinate OR 'nico 400' OR nico400 OR induracin OR nicolar OR nicocap OR wampocap OR nicobid OR '3 pyridinecarboxylic acid' OR enduracin OR niacinamide OR papulex OR 'vitamin b3' OR 'vitamin b 3' OR 'vitamin pp' OR nicotinamide OR enduramide OR nicobion OR '3 pyridinecarboxamide' OR nicotinsaureamid OR niaspan OR tredaptive OR 'antipellagra factor' OR niacor OR nicotinex OR vitb3 OR nicamid OR 'nicomide t' OR nicosedine
#18	'bile acid sequestrant'/exp OR 'colesevelam'/de OR 'colestyramine'/de OR 'colestipol'/de OR (bile NEAR/3 acid* NEAR/3 sequestrant*) OR (ba NEAR/3 sequestrant*) OR bas OR

	colesevelam OR cholestagel OR welchol OR lodalis OR 'gt 31104' OR 'gt31 104' OR gt31104 OR cholestyramine* OR colestyramin* OR questran* OR prevalite OR cuemid* OR quantalan* OR mk135 OR 'mk 135' OR colestipol OR colestid OR cholestabyl OR 'u-26597 a' OR 'u 26597 a' OR 'u26597 a' OR colestimide OR colestilan OR 'mci 196'
#19	bempedoi* AND acid* OR nexletol OR nexlizet OR nilemdo OR nustendi OR bempedoate OR etc1002 OR 'etc 1002' OR esp55016 OR 'esp 55016' OR '738606 46 7'
#20	'omega 3 fatty acid'/de OR 'fish oil'/de OR 'cod liver oil'/de OR omega3* OR 'omega 3*' OR 'fatty acid*' OR pufa OR 'n 3pufa*' OR n3pufa* OR dha OR docosahex* OR eicosapent* OR epa OR 'ethyl eicosapent*' OR ethyleicosapent* OR alphalinolen* OR 'alpha linolen*' OR linolenate* OR linolenic* OR ((n3 OR 'n 3' OR w3 OR 'w 3') NEAR/3 (oil* OR polyunsaturat*)) OR ((fish* OR cod) NEAR/2 oil*)
#21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	'randomized controlled trial'/exp OR 'randomization'/exp OR 'double blind procedure'/de OR 'triple blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'controlled clinical trial'/exp OR randomized:ab OR placebo:ab OR randomly:ab OR trial:ab OR groups:ab OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim
#23	#3 AND #21 AND #22
#24	('animal'/exp OR [animals]/lim) NOT ([humans]/lim OR 'human'/exp)
#25	#23 NOT #24 AND [english]/lim AND [2003-2022]/py

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No.	Searches
#1	TS=(PCSK9 OR PCSK-9)
#2	TS=((kexin* NEAR/3 "9") OR (subtilisin* NEAR/5 "9"))
#3	TS=((proprotein OR pro-protein) NEAR/3 convertase* NEAR/5 "9")
#4	TS=(NARC1 OR NARC-1)
#5	TS=((neur* OR apopt*) NEAR/5 convertase* NEAR/3 "1")
#6	**#5 OR #4 OR #3 OR #2 OR #1**
#7	TS=((("hydroxymethylglutaryl Coenzyme" OR "hydroxymethylglutaryl CoA" OR "HMG CoA") NEAR/5 inhib*) OR statin OR statins)
#8	TS=(anticholesterol$emic OR hypocholesterol$emic OR hypocholester$emic OR anticholester$emic)
#9	TS=((cholesterol OR lipid* OR LDL OR HDL OR TG OR TC OR triglyceride) NEAR/3 (reduc* OR lower* OR inhib* OR drug* OR agent*))
#10	TS=(Atorvastatin OR atorlip OR atovarol OR cardyl OR "ci 981" OR ci981 OR glustar OR lipibec OR lipitor OR liprimar OR liptonorm OR lowlipen OR sortis OR storvas OR tahor OR torvast OR totalip OR xarator OR "ym 548" OR ym548 OR zarator)
#11	TS=(Simvastatin OR Synvinolin OR "MK 733" OR MK733 OR Zocor OR avastinee OR cholestat OR clinfar OR colastatina OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR kavelor OR klonastin OR kolestevan OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR "nor vastina" OR normofat OR orovas OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simvacor OR simvahex OR simvalord OR simvastar OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR starzoco OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocord OR zovast OR inegy OR vytorin OR zetsim OR zintrepid OR cholib OR fenofibrate* OR "niacin simvastatin" OR simcor OR "rosiglitazone simvastatin" OR avandastat OR "sitagliptin simvastatin" OR sitagliptin phosphate* OR juvisync)
#12	TS=(Pitavastatin OR nisvastatin OR itavastatin OR alipza OR livalo OR livazo OR pitava OR ribar OR vezepra OR "P 872441" OR "NK 104" OR "nk104" OR "nks 104" OR nks104 OR lippiza OR nikita OR trolise OR zypitamag)
#13	TS=(Cerivastatin OR kazak OR rivastatin OR certa OR "bay w 6228" OR "bay w6228" OR baycol OR lipobay)

#14	TS=(Lovastatin OR mevinolin OR monacolin OR "6 Methylcompactin" OR "MK 803" OR MK803 OR mk0803 OR mevacor OR altocor OR altoprev OR artein OR belvas OR birotin OR cholestra OR cysin OR ellanco OR elstatin OR lipdip OR lipivas OR lofacol OR lomar OR lostatin OR lovacel OR lovacol OR lovalip OR lovalord OR lovastan OR lovasterol OR lovastin OR lovatadin OR lowachol OR lozutin OR medostatin OR meverstin OR mevinacor OR monakolin OR "msd 803" OR neolipid OR nergadan OR ovasta OR rodatin OR rovacor OR taucor OR advicor)
#15	TS=(Fluvastatin OR fluindostatin OR lescol OR "XU 62-320" OR "XU 62320" OR xu62320 OR canef OR cranoc OR "fractal lp" OR leucol OR lochol OR locol OR "sri 62320" OR sri62320 OR vastin)
#16	TS=(Pravastatin OR eptastatin OR vasten OR "CS 514" OR CS514 OR lipemol OR liplat OR "nu pravastatin" OR prareduct OR mevalotin OR pravachol OR elisor OR selektine OR pravacol OR pravasin OR lipostat OR "RMS 431" OR RMS431 OR "SQ 31000" OR SQ31000 OR "SQ 31,000" OR SQ31,000 OR bristacol OR astin OR cholespar OR epatostantin OR eptastatine OR kenstatin OR lipidal OR liprevil OR novales OR prascolend OR prastan OR prava OR pravaselect OR pravasine OR pravator OR pravyl OR sanaprav OR selipran OR stanidine OR vasopran OR xipral OR pravafenix)
#17	TS=(Rosuvastatin OR ZD4522 OR "ZD 4522" OR crestor OR rosuvas OR "s 4522" OR s4522 OR certriad)
#18	**#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**
#19	TS=(ezetimibe OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy OR "SCH 58235" OR SCH58235)
#20	TS=(fibric acid OR fibrate* OR gemfibrozil OR bezafibrate OR ciprofibrat* OR fenofibrate OR clofibrate OR asufibrat* OR befibrat* OR befizal OR bezacur OR bezafibratum OR bezafisal OR dezagen OR bezalande OR bezalex OR bezapuren OR bezastad OR bionolip OR cedur OR closer OR difaterol OR durabezur OR eulitop OR hadiel OR klestran OR liparol OR lipitrol OR lipocin OR lipox OR norlip OR polyzalip OR redalip OR sklerofibrate OR regadrin OR befizal OR bezamerck OR reducterol OR bezalip OR solibay OR cedur OR azufibrate OR difaterol OR lipox OR clofenapate OR clofibric acid OR clofibrinic acid OR livesan OR liparison OR durafenat OR supralip OR lofibra OR fenobeta OR lipantil OR tricor OR controlip OR gemfibrozil OR gemfibro* OR lipazil OR lopid OR nugemfibrozil OR apogemfibrozil)
#21	TS=(niacin OR nicotinic acid OR nicamin OR nicotinate OR "nico 400" OR nico-400 OR nico400 OR induracin OR nicolar OR nicocap OR wampocap OR nicobid OR "3 pyridinecarboxylic acid" OR 3-pyridinecarboxylic acid OR enduracin OR niacinamide OR papulex OR "vitamin b3" OR "vitamin b 3" OR vitamin pp OR nicotinamide OR enduramide

	OR nicobion OR "3 pyridinecarboxamide" OR 3-pyridinecarboxamide OR nicotinsaureamid OR Niaspan OR Tredaptive OR antipellagra factor OR niacor OR nicotinex OR vitb3 OR nicamid OR nicomide-t OR nicosedine)
#22	TS=((((bile NEAR/3 acid*) OR BA) NEAR/3 sequestrant*) OR BAS) OR TS=(Colesevelam OR Cholestagel OR Welchol OR Lodalis OR "GT 31104" OR GT-31104 OR GT31-104 OR "GT31 104" OR GT31104) OR TS=(Cholestyramine* OR Colestyramin* OR Questran* OR Prevalite OR Cuemid* OR Quantalan* OR MK-135 OR MK135 OR "MK 135") OR TS=(Colestipol OR Colestid OR Cholestabyl OR "U-26597 A" OR "U 26597 A" OR "U26597 A" OR Colestimide OR colestilan OR MCI-196)
#23	TS=(bempedoi* AND acid* OR nexletol OR nexlizet OR nilemdo OR nustendi OR bempedoate OR etc1002 OR "etc 1002" OR esp55016 OR "esp -55016" OR "738606 46 7")
#24	TS=(omega3* OR "omega 3*" OR "fatty acid*" OR pufa OR "n 3pufa*" OR n3pufa* OR dha OR docosahex* OR eicosapent* OR epa OR "ethyl eicosapent*" OR ethyleicosapent* OR alphalinolen* OR "alpha linolen*" OR linolenate* OR linolenic* OR ((n3 OR "n 3" OR w3 OR "w 3") NEAR/3 (oil* OR polyunsaturat*)) OR ((fish* OR cod) NEAR/2 oil*))
#25	**#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24**
#26	TS=(randomized OR placebo OR randomly OR trial OR groups)
#27	**#6 AND #25 AND #26** **and English (语种) and 入库时间: 2003-01-01 to 2022-12-31 (出版日期)**