SUPPLEMENTARY DATA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Study design
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.	Database search, study selection, data extraction and risk of bias assessment
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Database search, study selection, data extraction and risk of bias assessment
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.	Database search, study selection, data extraction and risk of bias assessment
Data collection	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked	Database

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process		independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	search, study selection, data extraction and risk of bias assessment
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.	Study design
	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.	Study design
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.	Database search, study selection, data extraction and risk of bias assessment
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.	Data synthesis and analysis
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)).	Study design
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Study design
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Data synthesis and analysis
	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.	Data synthesis and analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Data synthesis and analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Data synthesis and analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Data synthesis and analysis
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Data synthesis

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assessment			and analysis
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.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results
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.	Impact of lipid-lowering therapies on ASCVD according to coronary artery calcium
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Impact of lipid-lowering therapies on ASCVD according to coronary artery calcium
	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.	Impact of lipid-lowering therapies on ASCVD according to coronary artery calcium
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Impact of lipid-lowering therapies on ASCVD

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			according to coronary artery calcium
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Atherosclerotic cardiovascular disease risk stratification by coronary artery calcium score
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Limitations
	23c	Discuss any limitations of the review processes used.	Limitations
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
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.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Fundings
Competing interests	26	Declare any competing interests of review authors.	Conflict of Interest
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.	Methods

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table 1 of the supplementary data. Risk of bias assessment for individual studies.

Study name	Selection bias	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
The St. Francis Heart Study Waheed et al.,[13] 2016	-	+/-	+/-	-	-	+/-
Korean registry Hwang et al.,[14] 2015	+/-	+/-	-	-	-	+/-
The BioImage Study Mortenses et al.,[4] 2016	+/-	-	-	-	-	-
Walter Reed Army Medical Center study Mitchell et al.,[15] 2018	+/-	+/-	-	-	-	+/-
Multi-Ethnic Study of Atherosclerosis Budoff et al.,[9] 2018	+/-	-	-	-	-	-

Table 2 of the supplementary data. ASCVD incidence rates for each study overall and categorized by lipid-lowering therapy and CAC strata-

Study Name ASCVD First author. publication year	**No CAC**			**CAC 1-99**			**CAC ≥100**		
	Overall	**Lipid-lowering therapy**	**No lipid-lowering therapy**	**Overall**	**Lipid-lowering therapy**	**No lipid-lowering therapy**	**Overall**	**Lipid-lowering therapy**	**No lipid-lowering therapy**
Hwang et al.,[14] 2015									
Absolute proportion	0/0 (0)	0/0 (0)	0/0 (0)	132/5755 (2.3)	22/1265 (1.7)	110/4490 (2.5)	104/1733 (4.3)	15/427 (3.5)	89/1306 (6.8)
Incidence (1000 person/year)	-	-	-	10.4	9.2	7.9	27.3	11.3	35.9
Waheed et al.,[13] 2016									
Absolute proportion	0/0 (0)	0/0 (0)	0/0 (0)	0/96 (0)	0/44 (0)	0/52 (0)	85/894 (9.5)	36/437 (8.2)	49/457 (10.7)

Incidence (1000 person/year)	-	-	-	0	0	0	9.5	8.2	10.7
Mortenses et al.,[4] 2016									
Absolute proportion	15/1852 (0.8)	4/500 (0.8)	11/1352 (0.8)	25/1675 (1.5)	8/586 (1.4)	17/1089 (1.6)	98/2278 (4.3)	31/911 (3.4)	67/1367 (4.9)
Incidence (1000 person/year)	3.0	3.0	3.0	5.5	5.1	5.8	15.9	12.6	18.2
Mitchell et al.,[15] 2018									
Absolute proportion	214/9360 (2.3)	100/3742 (2.7)	114/5618 (2.0)	108/2877 (3.8)	76/1933 (3.9)	32/944 (3.4)	155/1407 (11.0)	123/1211 (10.2)	32/196 (16.3)
Incidence (1000 person/year)	2.3	2.7	2.0	3.8	3.9	3.4	11.0	10.2	16.3
Budoff et al.,[9] 2018									
Absolute proportion	109/3390 (3.2)	13/361 (3.6)	96/3029 (3.2)	141/1785 (7.9)	27/348 (7.8)	114/1437 (7.9)	247/1593 (15.5)	60/392 (15.3)	187/1201 (15.6)

Incidence (1000 person/year)	3.2	3.6	3.2	7.9	7.8	7.9	15.5	15.3	15.6

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium.

Number of events are provided as n° of events/n° of patients exposed. Incidence data are provided in person-year (n/N * years).

Table 3 of the supplementary data. Odds ratios (95% confidence intervals) for ASCVD occurrence categorized by CAC strata among patients on lipid-lowering therapy prior to CAC assessment

ASCVD OR (95%CI) for increasing CAC strata among patients on lipid-lowering therapy prior to CAC assessment				
CAC strata	**Mortenses et al.,[4] 2016**	**Mitchell et al.,[15], 2018**	**Budoff et al.,[9] 2018**	**POOLED**
CAC none	0.58 [0.17, 1.95]	0.67 [0.50, 0.91]	0.44 [0.23, 0.88]	0.57 [0.41, 0.73]
CAC 0-100	REF	REF	REF	REF
CAC >100	2.55 [1.16, 5.58]	2.76 [1.71, 4.46]	2.15 [1.33, 3.47]	2.18 [1.98, 2.39]

95%CI, 95% confidence interval; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; OR, odds ratio.

STUDY SEARCH

("calcium artery score" [tiab] OR "calcium score"[tiab] OR "CAC"[tiab]) AND ("statin" [tiab] OR "lipid lowering" [tiab] OR "preventive therapy" [tiab])

Guidelines for Deciding Whether Apparent Differences in Subgroup Response Are Real (Sun et al, JAMA 2014;311:405-411)

1) **Can Chance Explain the Subgroup Difference?**

   The observed subgroup differences in both unadjusted and adjusted analyses (figure 2 and figure 3) are not explained by chance as the p for interaction among subgroups are significant (*P* = .004 and .003: ie, the chance that a subgroup effect is identified by chance is of 0.4 and 0.1%, respectively).

2) **Is the subgroup difference consistent across studies?**

   Subgroup analyses were limitedly presented in the studies included in the present meta-analysis. Consistently with our results, the subgroup analysis presented by the study by Mitchell et al comparing patients with and without statin exposure, statin therapy was associated with reduced risk of ASCVD in patients with CAC (*P* = .015), but not in patients without CAC (*P* = .99). Moreover, the effect of statin use on ASCVD was significantly related to the severity of CAC (*P* < .0001 for interaction).

3) **Was the subgroup difference one of a small number of a priori hypotheses in which the direction was accurately prespecified?**

   Yes, it is. Indeed, it was the primary study hypothesis of the meta-analysis: ie, the interaction of CAC strata with the benefit of lipid-lowering therapy.

4) **Is there a strong preexisting biological rationale supporting the apparent subgroup effect?**

   Yes, there is a strong phyisiopathological rationale for the observed interaction of CAC strata with the benefit of lipid-lowering therapy. Specifically, patients with more extensive CAC burden have more extensive and more active atherosclerosis which may benefit from lipid-lowering therapy.

5) **Is the subgroup difference suggested by comparisons within rather than between studies?**

   Yes, a visual analysis of figure 2 and figure 3 suggests that the subgroup differences observed with the meta-analytic approach are consistent within individual studies.