


BMJ Open PCSK9 inhibitors for anti-inflammation in atherosclerosis: protocol for a systematic review and meta-analysis of randomised controlled trials

Jichang Luo,^{1,2} Wanying Liao,³ Xue Wang,⁴ Ran Xu,^{1,2} Wei Li,⁵ Wenjing Li,⁶ Kan Liu,⁷ Kaixun Huang,⁸ Yan Ma,^{1,2} Tao Wang ,^{1,2} Bin Yang,^{1,2} Liqun Jiao ^{1,2,9}

To cite: Luo J, Liao W, Wang X, *et al.* PCSK9 inhibitors for anti-inflammation in atherosclerosis: protocol for a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2022;**12**:e062046. doi:10.1136/bmjopen-2022-062046

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062046>).

JL, WL and XW are joint first authors.

Received 15 February 2022
Accepted 02 November 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Liqun Jiao;
liqunjiao@sina.cn and
Bin Yang;
yangbin_81@163.com

ABSTRACT

Introduction Atherosclerosis is the leading cause of cardiovascular disease (CVD), which is one of the most common causes of morbidity and mortality worldwide. Lipid accumulation and inflammation play a crucial role in the pathogenesis of atherosclerosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an emerging lipid-lowering agent reported as a potential anti-inflammation effect in the prevention of CVD. However, the anti-inflammatory effect is still elusive. Therefore, a systematic review and meta-analysis is needed to analyse the anti-inflammatory effect of PCSK9 inhibitors on atherosclerosis in practice.

Methods and analysis This protocol was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. We will include double-blind, randomised controlled trials that reported changes in the levels of inflammatory markers, with an intervention arm of PCSK9 inhibitors and a treatment duration of more than 2 weeks. The following databases will be mainly searched from 1 January 2003 to the formal search date: PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials. The primary aim is to assess the effect of PCSK9 inhibitors on inflammatory markers, including circulating inflammatory markers such as C-reactive protein, high-sensitivity C-reactive protein, white cell counts, IL-1 β , IL-6 and TNF- α and local inflammatory markers such as the most diseased segment target-to-background ratio of the index vessel in adult patients with atherosclerosis. We will assess the quality of evidence, heterogeneity and report bias following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination Due to the systematic review being based on published studies, no ethics approval is required. The study results will be presented at international conferences and published in a peer-reviewed journal.

PROSPERO registration number CRD42022297710.

BACKGROUND

Atherosclerosis, a chronic condition that begins in middle age and lasts lifelong, is the leading cause of cardiovascular disease, accounting for one of the most common

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review and meta-analysis will synthesise high-quality evidence from phase 2 or phase 3 double-blind randomised controlled trials.
- ⇒ The risk of bias will be evaluated using the Cochrane Collaboration criteria.
- ⇒ Sources of heterogeneity will be explored by subgroup and sensitivity analysis.

causes of morbidity and mortality worldwide.¹ Lipid metabolism disorders, especially low-density lipoprotein cholesterol (LDL-C), play a crucial role in the pathogenesis of atherosclerosis with lipid accumulation, oxidation and glycation in the subendothelium of the arterial wall.² Besides being a disorder of lipid accumulation, atherosclerosis is thought to be a process of chronic and progressive inflammation triggered by the interaction of LDL-C, monocyte-derived macrophages, T cells and the normal artery cells, as well as inflammatory cytokines like C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP), IL-1 β , IL-6 and TNF- α .³ Inflammatory activation may hasten the progression of atherosclerosis by damaging the skeleton of the fibrous cap, which may result in plaque rupture and cardiovascular events.⁴ Elevated levels of inflammatory biomarkers have been associated with an increased risk of cardiovascular events, and anti-inflammatory medications may help to minimise this risk.⁵ Recently, evidence from Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) reported that anti-inflammatory therapy significantly reduced hs-CRP levels without decreasing LDL-C levels, as well as decreased the primary cardiovascular events like non-fatal myocardial infarction, and non-fatal stroke and cardiovascular death after a



3.7-year follow-up period, supporting the inflammatory hypothesis of atherosclerosis.⁶

Although LDL-C reduction with lipid-lowering agents like statins targets primary or secondary prevention of cardiovascular diseases, many studies have indicated that these drugs' benefits go beyond lowering LDL-C. Evidence has suggested that statins' success in preventing cardiovascular events is not linearly or merely related to their hypo-lipidemic action for LDL-C reduction; in addition, their efficacy may be attributed to their capacity to attenuate systemic inflammation and hs-CRP levels.^{7 8} Similarly, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are elegant lipid-lowering agents for lowering LDL-C and other lipid parameters recently.^{9–11} Several high-level trials revealed that PCSK9 inhibitors and add-on statins reduced the mean percentage of LDL-C levels by approximately 60% compared with placebo or other lipid-lowering agents.^{12 13} A meta-analysis encompassing 35 randomised controlled trials (RCTs) and 45 539 patients disclosed that PCSK9 inhibitors reduced LDL-C by 60.94% and 31.32% compared with placebo and ezetimibe, respectively.¹⁴ In addition to their efficacy in lowering LDL-C, PCSK9 inhibitors are recently shown to have an anti-inflammatory effect in animal models and in vitro studies, like reducing the accumulation of macrophages and suppressing the production of proinflammatory cytokines.^{15–17} Moreover, PCSK9 inhibits stress response and inflammation gene expression in liver cells, implying that PCSK9 has an impact on metabolic pathways other than cholesterol metabolism.^{18 19} Studies on PCSK9 and extracellular vesicles (EV) in obese populations and human monocyte lines have shown that PCSK9 mediated the generation of EV and regulated EV-derived miRNAs, indicating that PCSK9 plays a role on inflammation milieu at the paracrine level, namely, among the components of the plaque.^{20 21}

Unfortunately, the anti-inflammatory effects of PCSK9 inhibitors for human atherosclerotic plaque are still controversial. Two meta-analyses published in 2016 and 2018 and several original studies found that PCSK9 inhibitors resulted in significant LDL-C reductions but had no effect on hs-CRP levels.^{22 23} However, compelling data from RCTs have revealed that the percentage change in macrophage grade is more prominent in the PCSK9 inhibitors group than in the control group (28.4% (35.3% to 19.0%) vs 10.2% (25.3% to 4.3%); $p=0.033$).²⁴ In addition, several studies have implied that hs-CRP, a liver-derived acute phase protein associated with systemic inflammation, may not correlate with local arterial wall inflammation. Local inflammatory markers are better indicators of proinflammation alterations in atherosclerotic plaque.^{25 26} Many related studies are focusing on other circulating inflammatory biomarkers such as CRP, white cell counts, IL-1 β , IL-6 and TNF- α , as well as local inflammatory markers of the arterial wall such as the most diseased segment target-to-background ratio of the index vessel measured by positron emission tomography/CT in the randomised control studies on PCSK9 inhibitors

for lipid-lowering.^{27–31} The anti-inflammatory impact of PCSK9 inhibitors has been inconsistently determined in these published studies employing various inflammatory biomarkers. Therefore, it is necessary for further analysis of literature, especially RCTs data, with a meta-analysis method to provide the highest-evidence guideline or recommendation of the anti-inflammatory effect of PCSK9 inhibitors on atherosclerosis in practice.

Objective

The primary objective of the current study is to assess the effect of PCSK9 inhibitors on the levels of inflammatory markers in patients with atherosclerosis. Inflammatory markers include circulating inflammatory markers such as hs-CRP, CRP, white cell counts, IL-1 β , IL-6 and TNF- α , and local inflammatory markers such as the most diseased segment target-to-background ratio of the index vessel. The secondary objectives are as follows: (1) to compare the anti-inflammatory effects of different types of PCSK9 inhibitors; (2) to determine the impact of treatment duration, participant characteristics and treatment strategy with monotherapy or combination therapy on the anti-inflammatory effects of PCSK9 inhibitors.

METHODS AND ANALYSIS

This protocol was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see online supplemental file 1), PRISMA-P Checklist).³² Any revision of this protocol and the entire review process will be promptly updated on the PROSPERO registration. This systematic review will be performed and reported using the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA extension statement for reporting systematic reviews incorporating meta-analyses of healthcare interventions.^{33 34}

Patients and public involvement

Patients and the public will not be directly involved in the study's design or execution.

Criteria for considering studies for this review

Types of studies

We will include phase 2 or phase 3 double-blind RCTs. Observational cohort, case-control, case series and registry studies will be excluded. Duplicate publications and other studies like non-human investigations will also be excluded. We will only consider studies published in English. No limits will be set for publication status.

Types of participants

We will consider studies involving adults (≥ 18 years old) with atherosclerotic cardiovascular diseases. Other comorbidities such as hyperlipidaemia, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease and obesity are allowed. The trials in children, those performed in patients without atherosclerosis, or animals will be excluded.

Types of interventions

All interventions involving the treatment of PCSK9 inhibitors will be considered for the analysis. We will also consider trials investigating the combination of other conventional lipid-lowering agents such as statins, ezetimibe, fibrates, bile acid sequestrants and nicotinic acid. Trials will be included in which the comparator was a placebo, no treatment or other conventional lipid-lowering agents when the experimental intervention was PCSK9 inhibitors alone or in combination with another lipid-lowering drug. There will be no restrictions on the types of PCSK9 inhibitors like monoclonal antibodies, small-interfering RNA (siRNA) and other types that will be considered. Studies with a treatment duration of less than 2 weeks will be eliminated.

Types of outcome measures

The trials that reported at least one of the following outcomes will be included.

Primary outcomes

At least one of the levels of inflammatory marker was reported at the beginning and end of the trial, or a net change in the levels of inflammatory markers.

Secondary outcomes

The changes in inflammatory markers were involved under treatment with different types of PCSK9 inhibitors, treatment duration, participant characteristics and treatment strategies such as monotherapy or combination therapy.

Inflammatory markers comprise circulating inflammatory markers such as hs-CRP, CRP, white cell counts, IL-1 β , IL-6 and TNF- α and local inflammatory markers like the most diseased segment target-to-background ratio of the index vessel.

Search methods for identification of studies

The following four databases will be primarily searched from 1 January 2003 to the formal search date: PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials. We will also search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for relevant RCTs. The reference lists of included studies and previously published systematic reviews will be reviewed to identify eligible studies. Further information will be obtained from published sources via exploring the grey literature sources or contacting the original authors when necessary. There will be no restrictions on publication status and type. A filter designed for retrieval of RCTs with maximised sensitivity will be applied.³⁵ Literature utilising subject search phrases in combination with the search strategy for identifying trials was developed by an experienced librarian and amended by another librarian according to the Peer Review of Electronic Search Strategies Checklist (see online supplemental file 2, search strategy).

Data extraction and analysis

Study selection

The two levels of study screening and selection will be carried out independently by two reviewers. Reviewers will assess if a study is eligible for inclusion in level one screening based on the title and abstract of articles acquired from the literature search. The full text of articles obtained from level one screening will be collected in level two screening, and those that meet the eligibility criteria will be included. When many studies present data from the same study population or multiple publications from the same study series are published in chronological sequence, the study with the most direct interventions or the largest sample size is retained. A pilot test based on predesigned test forms will be completed before each screening level to calculate inter-rater reliability. High agreement (80%) is required to start the formal screening (see online supplemental file 3, screening pilot-test form). Disagreements between the two reviewers will be handled by discussion or the involvement of a third reviewer if necessary. The study authors will be contacted for more information if there is ambiguity or insufficient data.

Data extraction and management

Two reviewers will extract data from relevant studies separately, with any disagreements handled by a third reviewer. The third reviewer will double-check the data. Only the appropriate arms will be included in RCTs with multiple arms. The following information will be extracted for each eligible study: trial name, first author, year of publication, PCSK9 inhibitors group and control group treatment methods, types and doses of PCSK9 inhibitors, treatment duration, follow-up period, number of patients, participant characteristics (mean or median age, proportion of male patients, LDL-C level, total cholesterol level and medical history), changes in the levels of inflammatory markers for each group. A similar pilot test to calculate inter-rater reliability is required to validate strong agreement (80%) between two reviewers. Similarly, disagreement between two reviewers will be resolved by discussion or by a third reviewer if necessary. We will contact the study authors for more information if there is any ambiguity or insufficient data.

Assessment of risk of bias in included studies

The risk of bias in eligible RCTs will be evaluated by two reviewers using the Cochrane Collaboration's tool.³³ If there is a disagreement, a third investigator will be consulted. We will assess the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias. The judgements were classified as 'low risk', 'high risk' and 'unclear risk' of bias.



Measure of treatment effect

As the change in the levels of inflammatory markers is a continuous variable, the treatment impact will be measured using mean difference (MD) with 95% CI. We will show the standardised mean difference (SMD) and 95% CI for data presented according to different scales.

Dealing with missing data

If essential research specifics or relevant data are missing, the principal authors of the listed studies will be contacted. We will send a reminder email if no response is received after 2 weeks. If the data are unavailable on requests finally, we will impute missing data using established methods such as informative missingness difference of means for continuous outcomes. Furthermore, a sensitivity analysis will be performed to confirm that our imputations do not affect the results.

Data synthesis and statistical analysis

Data synthesis

Only if the data are sufficient and treatment results, such as changes in the levels of inflammatory markers, are comparable, will we do meta-analyses using STATA (V.17, StataCorp, 2021); otherwise, the findings will be reported narratively. The levels of inflammatory markers will be estimated using MD with 95% CI or SMD with 95% CI.

Assessment of heterogeneity

We will use Q tests and I^2 statistics to assess clinical or methodological heterogeneity within and across treatment comparisons. In this study, either p -value < 0.10 or $I^2 > 50\%$ suggests significant heterogeneity, and a random-effects model will be applied. Sources of heterogeneity will be explored by subgroup and sensitivity analysis. Clinical heterogeneity will be assessed by examining differences in study designs, participant characteristics, the treatment effect and the overlap of CI on forest plots. Statistical heterogeneity among studies will be calculated using the I^2 statistics. If heterogeneity is not identified (p -value ≥ 0.10 or $I^2 \leq 50\%$), the Mantel-Haenszel fixed-effect model will be used to produce the pooled estimates of the treatment effect for each outcome.

Subgroup analysis and sensitivity analysis

If sufficient data are available, we will apply subgroup analysis to explore plausible explanations for heterogeneity, such as (1) types of PCSK9 inhibitors; (2) treatment duration and (3) treatment method: monotherapy or combination therapy. Sensitivity analyses will be conducted by excluding each study in turn and comparing the consistency of the results to test the robustness of our findings.

Assessment of report bias

Publication bias will be examined using Begg's rank correlation and Egger's weighted regression tests. The funnel plot method will be used if there are 10 or more studies. The applications will be investigated if asymmetry in the funnel plot is discovered.

Assessment of the certainty of the evidence

We will use the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach to assess the evidence's quality.³⁶ The strength of evidence will be classified as high, moderate, low or very low, depending on the risk of bias, consistency, directness, precision and publication bias. If a meta-analysis is not possible, the results will be presented in a narrative format.

Discussion

There is widespread agreement that atherosclerosis is a lipid accumulation disorder and inflammation disorder. Increasing studies have confirmed that inflammation is the important risk factor for the development and progression of atherosclerosis and future adverse cardiovascular events.³⁷ Anti-inflammation therapy is an effective strategy for preventing cardiovascular diseases, according to the CANTOS findings.⁶ There is evidence that statins, which are commonly used to lower cholesterol, have a pleiotropic effect by reducing inflammation and lowering LDL-C.^{38, 39} PCSK9 inhibitors are more effective than intensive statin therapy in lowering LDL-C levels and reducing the rate of severe adverse cardiovascular events, but their anti-inflammatory effects remain elusive. PCSK9 inhibitors have been shown in several studies to have a powerful impact of lipid-lowering and prevention of cardiovascular diseases without alteration of hs-CRP levels.^{22, 23} However, evidence from high-level data suggests that one of the fundamental mechanisms for clinical improvements from PCSK9 inhibitors may be more robust stabilisation of vulnerable plaque.⁴⁰ Moreover, studies showed that PCSK9 siRNA and PCSK9 vaccination could decrease the number of macrophages and vascular inflammation.^{16, 41} As a result, focusing on whether PCSK9 inhibitors can reduce inflammatory markers is clinical of great interest. In the current study, we will conduct a comprehensive analysis with recently available RCTs to provide the highest evidence of the anti-inflammatory effect of PCSK9 inhibitors.

Author affiliations

¹China International Neuroscience Institute (China-INI), Beijing, China

²Department of Neurosurgery, Xuanwu Hospital Capital Medical University, Beijing, China

³Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

⁴Medical Library, Xuanwu Hospital, Capital Medical University, Beijing, China

⁵Department of Neurosurgery, Liaocheng People's Hospital, Liaocheng, Shandong, China

⁶National Laboratory of Pattern Recognition Institute of Automation Chinese Academy of Sciences, Beijing, China

⁷First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan Province, China

⁸The Eighth Affiliated Hospital of Sun Yat-Sen University, Shenzhen, China

⁹Department of Interventional Radiology, Xuanwu Hospital, Capital Medical University, Beijing, China

Contributors LJ and BY developed the initial idea for this study. JL and WL contributed to the original draft. WX and RX developed and revised the search strategy. Weil, WenL, KL and KH will screen the potential studies independently, extract data from the included studies, assess the risk of bias and complete the

data synthesis. YM and TW will arbitrate in cases of disagreement and ensure the absence of errors. JL, WaL and XW contributed equally to this article. All authors reviewed and approved the publication of the protocol.

Funding This work was supported by the Beijing Science and Technologic Project (Z201100005520019).

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 required.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Tao Wang <http://orcid.org/0000-0003-1225-0173>

Liqun Jiao <http://orcid.org/0000-0003-4982-6295>

REFERENCES

- Joseph P, Leong D, McKee M, *et al*. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. *Circ Res* 2017;121:677–94.
- Yurtseven E, Ural D, Baysal K, *et al*. An update on the role of PCSK9 in atherosclerosis. *J Atheroscler Thromb* 2020;27:909–18.
- Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res* 2019;124:315–27.
- Libby P, Buring JE, Badimon L, *et al*. Atherosclerosis. *Nat Rev Dis Primers* 2019;5:56.
- Bohula EA, Giugliano RP, Leiter LA, *et al*. Inflammatory and cholesterol risk in the Fourier trial. *Circulation* 2018;138:131–40.
- Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.
- Ridker PM, Danielson E, Fonseca FAH, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
- Ridker PM, Lüscher TF. Anti-Inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;35:1782–91.
- Sabatine MS, Giugliano RP, Wiviott SD, *et al*. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med Overseas Ed* 2015;372:1500–9.
- Giugliano RP, Pedersen TR, Saver JL, *et al*. Stroke prevention with the PCSK9 (proprotein convertase Subtilisin-Kexin type 9) inhibitor evolocumab added to statin in high-risk patients with stable atherosclerosis. *Stroke* 2020;51:1546–54.
- Murphy SA, Pedersen TR, Gaciong ZA, *et al*. Effect of the PCSK9 inhibitor evolocumab on total cardiovascular events in patients with cardiovascular disease: a Prespecified analysis from the Fourier trial. *JAMA Cardiol* 2019;4:613–9.
- Sabatine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–22.
- Schwartz GG, Steg PG, Szarek M, *et al*. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097–107.
- Karatasakis A, Danek BA, Karacsonyi J, *et al*. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc* 2017;6. doi:10.1161/JAHA.117.006910. [Epub ahead of print: 09 Dec 2017].
- Schuster S, Rubil S, Endres M, *et al*. Anti-PCSK9 antibodies inhibit pro-atherogenic mechanisms in APOE*3Leiden.CETP mice. *Sci Rep* 2019;9:11079.
- Landlinger C, Pouwer MG, Juno C, *et al*. The AT04A vaccine against proprotein convertase subtilisin/kexin type 9 reduces total cholesterol, vascular inflammation, and atherosclerosis in APOE*3Leiden.CETP mice. *Eur Heart J* 2017;38:2499–507.
- Karagiannis AD, Liu M, Toth PP, *et al*. Pleiotropic anti-atherosclerotic effects of PCSK9 InhibitorsFrom molecular biology to clinical translation. *Curr Atheroscler Rep* 2018;20:20.
- Lan H, Pang L, Smith MM, *et al*. Proprotein convertase subtilisin/kexin type 9 (PCSK9) affects gene expression pathways beyond cholesterol metabolism in liver cells. *J Cell Physiol* 2010;224:n/a–81.
- Wiciński M, Żak J, Malinowski B, *et al*. Pcsk9 signaling pathways and their potential importance in clinical practice. *Eprma J* 2017;8:391–402.
- Macchi C, Greco MF, Favero C, *et al*. Associations among PCSK9 levels, Atherosclerosis-Derived extracellular vesicles, and their miRNA content in adults with obesity. *Front Cardiovasc Med* 2021;8:785250.
- Scalise V, Lombardi S, Sanguinetti C, *et al*. A novel prothrombotic role of proprotein convertase subtilisin kexin 9: the generation of procoagulant extracellular vesicles by human mononuclear cells. *Mol Biol Rep* 2022;49:4129–34.
- Cao Y-X, Li S, Liu H-H, *et al*. Impact of PCSK9 monoclonal antibodies on circulating hs-CRP levels: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2018;8:e022348.
- Sahebkar A, Di Giosia P, Stamerra CA, *et al*. Effect of monoclonal antibodies to PCSK9 on high-sensitivity C-reactive protein levels: a meta-analysis of 16 randomized controlled treatment arms. *Br J Clin Pharmacol* 2016;81:1175–90.
- Sugizaki Y, Otake H, Kawamori H, *et al*. Adding alirocumab to rosuvastatin helps reduce the vulnerability of Thin-Cap Fibroatheroma: an ALTAIR trial report. *JACC Cardiovasc Imaging* 2020;13:1452–4.
- Ruscica M, Tokgözoğlu L, Corsini A, *et al*. Pcsk9 inhibition and inflammation: a narrative review. *Atherosclerosis* 2019;288:146–55.
- Verweij SL, Duivenvoorden R, Stiekema LCA, *et al*. Ccr2 expression on circulating monocytes is associated with arterial wall inflammation assessed by 18F-FDG PET/CT in patients at risk for cardiovascular disease. *Cardiovasc Res* 2018;114:468–75.
- Hoogeveen RM, Opstal TSJ, Kaiser Y, *et al*. PCSK9 Antibody Alirocumab Attenuates Arterial Wall Inflammation Without Changes in Circulating Inflammatory Markers. *JACC Cardiovasc Imaging* 2019;12:2571–3.
- Scicali R, Di Pino A, Ferrara V, *et al*. Effect of PCSK9 inhibitors on pulse wave velocity and monocyte-to-HDL-cholesterol ratio in familial hypercholesterolemia subjects: results from a single-lipid-unit real-life setting. *Acta Diabetol* 2021;58:949–57.
- Baruch A, Mosesova S, Davis JD, *et al*. Effects of RG7652, a monoclonal antibody against PCSK9, on LDL-C, LDL-C subfractions, and inflammatory biomarkers in patients at high risk of or with established coronary heart disease (from the phase 2 EQUATOR study). *Am J Cardiol* 2017;119:1576–83.
- Burggraaf B, Pouw NMC, Arroyo SF, *et al*. A placebo-controlled proof-of-concept study of alirocumab on postprandial lipids and vascular elasticity in insulin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2020;22:807–16.
- Landmesser U, Haghikia A, Leiter LA, *et al*. Effect of inclisiran, the small-interfering RNA against proprotein convertase subtilisin/kexin type 9, on platelets, immune cells, and immunological biomarkers: a pre-specified analysis from ORION-1. *Cardiovasc Res* 2021;117:284–91.
- Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2.0 [updated March 2021]. *The Cochrane Collaboration*, 2021. Available: <http://handbook.cochrane.org/>
- Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
- Higgins J, Thomas J, Chandler J. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). *Cochrane*, 2021. Available: www.training.cochrane.org/handbook



- 36 Atkins D, Best D, Briss PA. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
- 37 Bäck M, Yurdagul A, Tabas I, *et al.* Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. *Nat Rev Cardiol* 2019;16:389–406.
- 38 Robinson JG, Smith B, Maheshwari N, *et al.* Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855–62.
- 39 Robinson JG. Models for describing relations among the various statin drugs, low-density lipoprotein cholesterol lowering, pleiotropic effects, and cardiovascular risk. *Am J Cardiol* 2008;101:1009–15.
- 40 Omori H, Ota H, Hara M, *et al.* Effect of PCSK-9 inhibitors on lipid-rich vulnerable coronary plaque assessed by near-infrared spectroscopy. *JACC Cardiovasc Imaging* 2020;13:1639–41.
- 41 Tang Z-H, Peng J, Ren Z, *et al.* New role of PCSK9 in atherosclerotic inflammation promotion involving the TLR4/NF- κ B pathway. *Atherosclerosis* 2017;262:113–22.