

# BMJ Open Protocol for systematic review and meta-analysis: impact of statins as immune-modulatory agents on inflammatory markers in adults with chronic diseases

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**To cite:** Sabeel S, Motaung B, Ozturk M, *et al.* Protocol for systematic review and meta-analysis: impact of statins as immune-modulatory agents on inflammatory markers in adults with chronic diseases. *BMJ Open* 2020;**10**:e039034. doi:10.1136/bmjopen-2020-039034

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-039034>).

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Received 02 April 2020  
Revised 02 June 2020  
Accepted 25 June 2020



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## ABSTRACT

**Introduction** Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, are lipid-lowering agents that are central in preventing or reducing the complications of atherosclerotic cardiovascular disease. Because statins have anti-inflammatory properties, there is considerable interest in their therapeutic potential in other chronic inflammatory conditions. We aim to identify the statin with the greatest ability to reduce systemic inflammation, independent of the underlying disease entity.

**Methods and analysis** We aim to conduct a comprehensive search of published and peer-reviewed randomised controlled clinical trials, with at least one intervention arm of a Food & Drug Administration-licensed or European Medicines Agency-licensed statin and a minimum treatment duration of 12 weeks. Our objective is to investigate the effect of statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) on lipid profile, particularly, cholesterol low-density lipoprotein and inflammation markers such as high-sensitive C reactive protein (hsCRP), CRP, tumour necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-8, soluble cluster of differentiation 14 (sCD14) or sCD16 in adults, published in the last 20 years (between January 1999 and December 2019). We aim to identify the most potent statin to reduce systemic inflammation and optimal dosing. The following databases will be searched: Medline, Scopus, Web of Science and Cochrane Library of Systematic Reviews. The risk of bias of included studies will be assessed by Cochrane Risk of Bias Tool and Quality Assessment Tool for Quantitative Studies. The quality of studies will be assessed, to show uncertainty, by the Jadad Score. If sufficient evidence is identified, a meta-analysis will be conducted with risk ratios or ORs with 95% CIs in addition to mean differences.

**Ethics and dissemination** Ethics approval is not required as no primary data will be collected. Results will be presented at conferences and published in a peer-reviewed journal.

**PROSPERO registration number** CRD42020169919

## INTRODUCTION

Statins are US Food & Drug Administration (FDA) approved lipid-lowering drugs

## Strengths and limitations of this study

- This study will include randomised controlled clinical trials to determine the most effective statin on the combined reduction of lipid profile and inflammatory biomarkers.
- High-quality clinical trials will be reviewed accurately to generate reliable evidence.
- This study will be conducted following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines.
- Variation of statin doses among included studies will likely produce heterogeneity that will subsequently reduce the sample size of the meta-analysis.

(table 1) that have been on the market for more than 30 years<sup>1</sup> and are widely prescribed to patients who are at high risk of cardiovascular diseases.<sup>2</sup> Statins exert their function via inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase which converts HMG-CoA into L-mevalonate resulting in reduced cholesterol biosynthesis.<sup>3</sup> The cholesterol biosynthesis inhibition via statins results in the upregulation of low-density lipoprotein (LDL) receptors on the cell surface which consequently leads to increased uptake and clearance of LDL in the circulating blood. This ultimately lowers LDL-cholesterol (LDL-C) and decreases the risk associated with lipoprotein deposition in the arterial wall and progression to atherosclerosis and vascular disease. In addition to statins' LDL-C lowering ability, statins also inhibit protein prenylation,<sup>4</sup> which is an important biological process that mediates protein-protein interaction and anchoring of cell membrane proteins.<sup>5</sup> The ability of statins to inhibit isoprenoids, important metabolites in the protein prenylation pathway, accounts

**Table 1** List of statins as a single-ingredient product licensed by the Food & Drug Administration and European Medicines Agency

Pharmacokinetic parameters												
Statin	Solubility	Type	Synthetic state	Cytochrome P450 subclass	Half-life (hours)	Clearance (L/hour)		Hepatic extraction		Excretion		
						Systemic	Oral	Renal	Hepatic		Urine	Faecal
Atorvastatin	Lipophilic	Fully synthetic	Active drug	CYP3A4	Mean* 17.8 Rangef 13.8–20.7 Dose\$: 20, 40, 80mg REF: 61 62	157		>70%	1.20%	70%		
Lipitor†						REF: 58		REF: 59	REF: 58	REF: 60		
Cerivastatin	Lipophilic	Fully synthetic	Active drug	CYP2C8 and CYP3A4	Mean* 2.96 Rangef 2.2–4.0 Dose\$: 0.2 to 0.3mg REF: 63–65	13			24%–30%	70%		
Lipobay†¶						REF: 63		REF: 66 67	REF: 66 67	REF: 66 67		
Fluvastatin	Lipophilic	Natural statin	Active drug	CYP2C9 some CYP2C8	Mean* 1.9 Rangef 1.5–2.4 Dose\$: 40 to 80mg REF: 73–76	68	120–180	69	73%	6%	93%	
Lescof‡						REF: 68	REF: 69 70	REF: 71	REF: 72	REF: 68	REF: 68	
Lovastatin	Lipophilic	Natural statin	Prodrug	CYP3A4	Mean* 2.7 Rangef 2.6–2.8 Dose\$: 20 to 40mg REF: 76 78 80	18–75	175–351	69%	9.60%	83.20%		
Mevacor†**						REF: 71	REF: 69 77 78 78	REF: 79	REF: 71	REF: 71		
Pitavastatin	Lipophilic	Fully synthetic	Active drug	Partially: CYP2C8 and CYP2C9	Mean* 10.7 Rangef 6.9–13.1 Dose\$: 1, 2, 4 mg REF: 81–84 86 87	16–26			15%	79%		
Livalof‡						REF: 81–84	REF: 81–84	REF: 85	REF: 85	REF: 85		
Rosuvastatin	Hydrophilic	Fully synthetic	Active drug	Partially: CYP2CP and CYP19	Mean* 14.2 Rangef 10.1–24.4 Dose\$: 5, 10, 20, 40mg REF: 88–93	49	273–281	82	12	63%	5%–10%	90%
Crestor†						REF: 94	REF: 88	REF: 95	REF: 94	REF: 94 96	REF: 96	
Pravastatin	Hydrophilic	Semisynthetic	Active drug	None	Mean* 2.17 Rangef 1.6–2.6 Dose\$: 10, 20, 40mg REF: 80 97 100–103	57		24–27	46%–66%	20%	71%	
Pravachol†						REF: 97	REF: 97	REF: 99	REF: 97	REF: 97	REF: 97	
Simvastatin	Lipophilic	Semisynthetic	Prodrug	CYP3A4	Mean* 4.6 Rangef 1.6–7.9 Dose\$: 20, 40, 60mg REF: 92 105 106 109–115	32	2000–3100	>79%	13%	58%		
Zocor†						REF: 104	REF: 105–107	REF: 79	REF: 104 108	REF: 104 108	REF: 104 108	

Continued

Table 1 Continued

Statin	Solubility	Type	Synthetic state	Cytochrome P450 subclass	Pharmacokinetic parameters		Clearance (L/hour)		Excretion			
					Half-life (hours)	Systemic	Oral	Hepatic	Renal	Hepatic extraction	Urine	Faecal
Cerivastatin is withdrawn from the market and lovastatin is not licensed in Great Britain and Switzerland *Mean calculated as the average of the means of the cited references. †Range of the means from the cited references. ‡Common brand name. §Half-life reported from indicated doses from the cited references. ¶Withdrawn from the market due to rhabdomyolysis in 2001. **Not commonly prescribed anymore and not licensed in Great Britain and Switzerland.												

for their lipid-independent pleiotropic effects.<sup>6 7</sup> Indeed statins have been reported to have anti-inflammatory, antioxidant antiproliferative and immunomodulatory effects independent of their cholesterol-lowering ability.<sup>8</sup> The reported vascular effects of statins are wide-ranging and include improvement of endothelial functioning, decreasing oxidative stress and maintenance of coronary artery plaque stability.<sup>8</sup> Statins may also lower the risk of liver cancer.<sup>9</sup> The anti-inflammatory effects vary among the different types of currently licensed statins with various meta-analyses reporting differential efficacy in reducing inflammation in chronic obstructive pulmonary disease (COPD).<sup>10</sup> Statins (table 1) are categorised into two main groups according to their solubility: (1) hydrophilic statins which include pravastatin and rosuvastatin and these display high hepato-selectivity with increased first-pass effect and (2) lipophilic statins which are characterised by passive diffusion into cells; these include atorvastatin, simvastatin, lovastatin, fluvastatin, pitavastatin and cerivastatin.<sup>11</sup>

### Statins and inflammation

Inflammatory responses to various clinical conditions result in elevated secretion and activity of acute inflammatory proteins such as C-reactive protein (CRP). In the liver, CRP is mainly secreted by hepatocytes in response to interleukin-6 (IL-6).<sup>12</sup> Increased secretion of IL-6 and CRP further exacerbate the inflammatory milieu through secretion of pro-inflammatory cytokines such as tumour necrosis factor (TNF), activation of the complement pathway, apoptosis, phagocytosis and nitric oxide release.<sup>13</sup> Previous clinical trials have reported statin therapy to reduce CRP levels through an LDL-C independent mechanism,<sup>14 15</sup> resulting in better clinical outcomes in patients with reduced CRP.<sup>16</sup> In addition, atorvastatin therapy was shown to reduce inflammatory biomarkers such as high-sensitive CRP (hsCRP) and IL-6 in patients with unstable angina who received the percutaneous coronary intervention and furthermore reduced cardiac troponin I and creatine kinase muscle brain suggesting a reduction in cardiac myocyte necrosis.<sup>17</sup> Additionally, the PRINCE randomised controlled trial (RCT) reported pravastatin (40 mg/day) therapy to have a significant reduction in CRP levels following 12 and 24 weeks of treatment.<sup>14</sup> Statin therapy further resulted in the downregulation of other inflammatory biomarkers, such as IL-8 and sCD14, in patients with coronary artery inflammation.<sup>18 19</sup> Currently it is not fully elicited on how different types of statins (hydrophilic or lipophilic, table 1) or the treatment duration differentially affect immune responses.

### Mechanisms to reduce inflammation

Statins are selectively taken up by hepatocytes and decrease inflammatory responses by regulating the expression of various cell surface molecules/receptors, transcription factors, cytokines, chemokines and other soluble inflammatory mediators.<sup>20</sup> Furthermore, their ability to be taken up by other cell types, including immune cells, depending

on the expression of cell membrane transport proteins and their chemical properties.<sup>11 21</sup> Statins can enter their target cells either through passive diffusion<sup>11</sup> or active transport which involves transmembrane proteins within the organic anionic-transporting polypeptide<sup>21 22</sup> and Na<sup>+</sup>taurocholate cotransporting polypeptides groups.<sup>23</sup>

#### Effects on cell surface receptor

Even though statins were shown to have no effect on peripheral frequencies of circulating CD14<sup>++</sup>CD16<sup>-</sup>, CD14<sup>++</sup>CD16<sup>+</sup> and CD14<sup>+</sup>CD16<sup>++</sup> monocyte subsets, statins were shown to reduce expression of cell surface receptors such as vascular endothelial growth factor receptor-2, toll-like receptor (TLR)-4 and tyrosine kinase receptor Tie2 which are involved in proliferation, migration and pathogen recognition within all monocyte populations.<sup>24</sup> Furthermore, statins downregulate the expression of TLR-2, human leukocyte antigen-DR and CC-chemokine receptor-2 on monocytes, while increasing peroxisome proliferator activated receptor- $\gamma$  activity, which enhances their anti-inflammatory properties.<sup>17 25</sup> The ability of statins to reduce chemokine and chemokine receptor expression on human vascular endothelial cells and human primary macrophages is achieved via inhibition of the isoprenoid geranylgeranyl pyrophosphate pathway.<sup>26</sup>

#### Effect on cell signalling

Statins are documented to affect cellular functionality of both monocytes and T cells through altering activation of lymphocyte function-associated antigen (LFA)-1 integrin molecules that are involved in lymphocyte adhesion, migration and transduction of co-stimulatory signals to T cells during antigen presentation.<sup>27</sup> Activation of LFA-1 integrin molecules leads to conformational changes in their structures, thus increasing their binding affinity for their respective substrates, which further enhances pro-inflammatory responses.<sup>28</sup> However, cellular uptake of statins is reported to inhibit these conformational changes in LFA-1 molecules and further enhance their anti-inflammatory properties.<sup>27</sup> Statins also modulate immune responses through alteration of cell-to-cell interaction. Here statins suppress monocyte-derived dendritic cells resulting in reduced T cell activation, proliferation and T helper differentiation.<sup>25</sup>

#### Downstream effects on soluble biomarkers

Statins inhibit monocyte chemoattractant protein-1 secretion, resulting in decreased leucocyte recruitment during inflammation.<sup>29</sup> Statins suppress the production of pro-inflammatory cytokines such as IL-6 and IL-8 in IL-1 $\beta$ -stimulated synoviocytes from rheumatoid arthritis patients via interference in protein prenylation and nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway.<sup>30</sup>

#### Classification of statins

Statins are classified based on several different factors.

**Source of origin:** They are classified as natural, semi-synthetic or fully synthetic (table 1). Natural statins are acquired from fungal fermentation and these include

lovastatin. Simvastatin and pravastatin are classified as semisynthetic statins because they are produced through direct alkylation of lovastatin and hydroxylation of mevastatin, respectively. Fully synthetic statins are produced from different substrates and these include pitavastatin, rosuvastatin, fluvastatin, atorvastatin and cerivastatin.<sup>11</sup>

**Pharmacological properties:** Two pharmacological properties differentiate statins; they are either prodrugs or active drugs (table 1). Prodrug statins include lovastatin and simvastatin; they are administered in an inactive state and are activated through hydrolysis by liver enzymes. Atorvastatin, cerivastatin, fluvastatin and pravastatin are administered as active drugs.<sup>11</sup>

**Physiochemical properties:** Statins are classified as lipophilic or hydrophilic (table 1). Atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin are relatively lipophilic statins as they dissolve efficiently in lipid/fat solution. Cytochrome P450 enzymes metabolise most lipophilic statins except pitavastatin, which is only partially metabolised by this pathway. Hydrophilic statins such as rosuvastatin and pravastatin are not significantly metabolised by the cytochrome P450 system.<sup>11</sup> Pravastatin and rosuvastatin are classified as hydrophilic statins as they dissolve efficiently in water. Pravastatin and rosuvastatin are excreted largely as the parent compound into faeces, urine and bile.<sup>31 32</sup>

**Liver selectivity:** The hepato-selective processing of statins is defined by their solubility profile; therefore, lipophilic statins diffused passively through hepatocyte cell membranes, whereas hydrophilic statins' uptake occurs through carrier transmembrane proteins.<sup>11</sup>

#### Statins in clinical conditions other than cardiovascular disease

##### Inflammation

Statin therapy has been reported to have a wide range of potentially beneficial effects. These include the improved clinical outcome of chronic kidney disease in patients presenting with acute coronary syndrome.<sup>33</sup> Statins also reduced mortality in patients with cirrhosis with bacteraemia and pneumonia.<sup>34</sup> Additionally, a 2-year treatment period with atorvastatin was associated with milder disease progression in patients with relapsing-remitting multiple sclerosis.<sup>35</sup> However, a study by Birnbaum *et al* reported that disease progression was exacerbated by atorvastatin combined with beta interferon in patients with multiple sclerosis.<sup>36</sup> Moreover, statin users developed significantly less uveitis.<sup>37</sup> Atorvastatin and rosuvastatin also inhibited the micro-inflammatory state and improved the nutritional status in patients who had maintenance haemodialysis.<sup>38</sup> In a retrospective observational study, pitavastatin usage significantly decreased the mortality risk in Japanese patients who had haemodialysis.<sup>39</sup> However, Palmer *et al* published a systemic review of RCTs and reported statins to be associated with uncertain adverse events in adults treated with dialysis regardless of serum cholesterol levels; furthermore, statin treatment showed no beneficial effects on mortality and cardiovascular events for patients

who had dialysis.<sup>40</sup> Rosuvastatin therapy was shown to reduce the levels of inflammatory markers, such as IL-6 and hsCRP, leading to resolved systemic inflammation and improved endothelial-dependent vascular function in patients with COPD.<sup>41</sup> Furthermore, a 6-month atorvastatin (80 mg) therapy improved cough on a quality-of-life scale in patients with bronchiectasis.<sup>42</sup>

### Cancer

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) RCT reported the effect of statins; specifically simvastatin, lovastatin, atorvastatin and fluvastatin in the reduction of inflammatory responses in both acute and chronic prostate inflammation.<sup>43</sup> Furthermore, in a retrospective cohort study, patients with COPD had a lower risk of prostate cancer following simvastatin, atorvastatin, pravastatin, fluvastatin and lovastatin therapy.<sup>44</sup> Inversely, an observational study by Emilsson *et al* that used observational data from the Surveillance, Epidemiology and End Results (SEER)-Medicare Databases on 17372 patients with cancer, reported that treatment with statins within 6 months after cancer diagnosis did not improve patients' survival rates when followed up for 3 years.<sup>45</sup>

### Central nervous system

Statins have a major effect on the central nervous system, particularly on cognition and neurological disorders and may decrease the risk of Alzheimer's disease (AD) and Parkinson's disease through direct impact on neurodegeneration and microglia, respectively.<sup>46</sup> However, the Lipitor's effect in Alzheimer's dementia (LEADc) RCT showed that even though atorvastatin (80 mg/day) treatment was well tolerated without unexpected adverse events in patients with AD, this treatment did not have significant beneficial effects on AD over a 72-week period.<sup>47</sup> Additionally, Sano *et al* further showed in an RCT that despite a significant reduction in cholesterol, simvastatin (20 mg/day) treatment did not prevent the progression of symptoms in individuals with mild to moderate AD.<sup>48</sup>

### Infection

Statins are reported to have a great effect on vaginal microbiome via reduced proportions of *Gardnerella vaginalis* and increased proportions of beneficial lactobacilli.<sup>49</sup> In addition, statins diminished the risk of infections in patients with type 2 diabetes.<sup>50</sup> Inversely, in patients with dementia statin therapy was associated with increased risk of infection.<sup>51</sup> However, it was reported that statin use in patients with asthma chronic pulmonary disease overlap syndrome was associated with lower tuberculosis (TB) and pneumonia risks after adjustment for multiple confounding factors.<sup>52</sup> Statin use was also associated with a lower risk of active TB.<sup>53 54</sup> Statin therapy also reduced the mycobacterial growth in human macrophages and mice by induction of autophagy and phagosome maturation.<sup>55</sup> Furthermore, many studies have stated the potential use of statins as host-directed therapy against

infectious diseases caused by viruses, protozoa, fungi and bacteria.<sup>56</sup>

Most of the data on statins as therapeutic agents originate from observational studies. This further highlights the need to perform RCTs to evaluate statins' immunomodulatory effects independent of their cholesterol-lowering ability. This protocol describes the investigation of commonly available statins (table 1) atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin focusing on their effect to reduce systemic inflammation in humans. Here, cerivastatin and lovastatin will be excluded due to decommissioned status from the market and the lack of license in Great Britain and Switzerland, respectively. This systematic review will address the hypothesis that pravastatin and rosuvastatin are inferior to other statins in reducing systemic inflammation due to increased first-pass effect.

## OBJECTIVES

### Primary objective

To identify the type of statin with the best potential to reduce systemic inflammation (statin type stratification).

### Secondary objective

To identify the optimal dose for each statin to reduce systemic inflammation (statin dose stratification).

## METHODS AND DESIGN

### Population

The systematic review will include high-quality RCTs on adults of at least 18 years of age who have been treated with either atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin, and in whom LDL-C, and at least one of the following markers of systemic inflammation: hsCRP, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, sCD14 or sCD16 are measured before and after statin treatment.

### Patient and public involvement

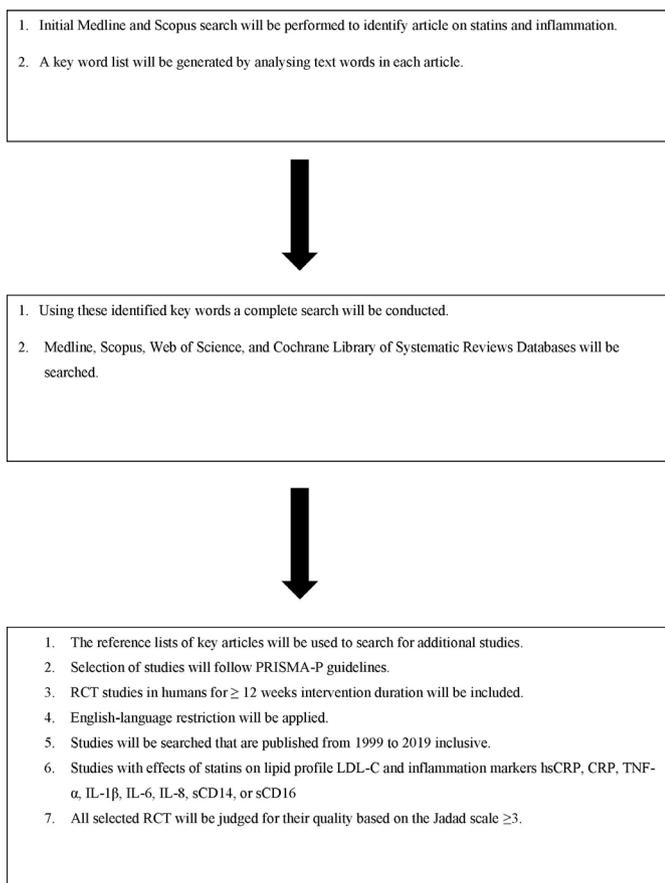
This is a systemic review and meta-analysis protocol which will address the anti-inflammatory effects of statins. This study does not involve patients and/or the public at any stage as primary data will not be collected.

### Study design

This systematic review will consider published and peer-reviewed randomised controlled clinical trials with at least one intervention arm of an FDA-licensed or European Medicines Agency (EMA)-licensed statin and a minimum treatment duration of 12 weeks.

### Search strategy

The search strategy (see online supplementary file 1) aims to identify published and peer-reviewed articles with available full text. A stepwise approach will identify the selected articles. As indicated in figure 1, an initial limited search of Medline and Scopus will be undertaken; this will be followed by the analysis of the text words contained in



**Figure 1** A schematic process of the systemic review. CRP, C reactive protein; hsCRP, high-sensitive C reactive protein; IL, interleukin; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol; RCT, randomised controlled clinical trial; TNF- $\alpha$ , tumour necrosis factor alpha.

the titles and abstracts, and of the index terms used to describe each article. A second search, using all identified keywords and index terms, will then be undertaken across all included databases. In the third step, the reference lists of key articles will be searched for additional studies. Studies will be restricted to the English language and to those published from 1999 to 2019, inclusive. The databases that will be searched are Medline, Scopus, Web of Science and Cochrane Library of Systematic Reviews.

### Eligibility criteria

#### Inclusion criteria

1. RCTs in humans.
2. Adults of at least 18 years of age.
3. At least one intervention arm including an FDA-licensed or EMA-licensed statin.
4. Minimum treatment duration of 12 weeks.
5. Studies that report the effects of statins on lipid profile LDL-C and inflammation markers hsCRP, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, sCD14 or sCD16.
6. Publication year: January 1999 to December 2019.

#### Exclusion criteria

1. RCT including participants with malignancies.

2. RCT including participants with autoimmune diseases.
3. RCT with cerivastatin (decommissioned from the market) or lovastatin (not commonly prescribed anymore and its usage is associated with more risks than beneficial effects) as intervention therapy.
4. Genetic studies.

### Study selection

The primary selection of publications will depend on the information contained in their titles and abstracts and will be conducted by two independent investigators and reported using Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (see online supplementary file 2). When the reviewers disagree, the article will be re-assessed by a third reviewer.

### Quality assessment

Two reviewers will independently verify selected articles to reduce the source of bias. All selected RCTs will be graded for their quality based on the Jadad Scale (see online supplementary file 3), the Oxford quality scoring system which is a widely used checklist for classification of quality of evidence.<sup>57</sup>

### Risk of bias assessment

Two reviewers will assess the risk of bias, based on the Cochrane Risk of Bias Tool for RCTs (see online supplementary file 4). The source of bias will be judged as high, low or unclear for the following domains: random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting of outcome and other sources of bias.

### Data extraction

Quantitative and qualitative data will be extracted from selected papers: higher scores in grading, low risk in the evaluation and depending on publication bias tool used. The data extracted will include three domains: (1) identification of the study (year publication, first author's name, PubMed identification number, title, journal name and impact factor); (2) methodology (study type, co-medication with statin intervention, target population (median/mean age, gender distribution, race), target condition, comorbidities, statin, type, dose, duration) and (3) outcomes (change (or relevant data to estimate change) in lipid profile LDL-C and inflammation markers hsCRP, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, sCD14 or sCD16). For data extraction, two independent Microsoft Excel spreadsheets will be compiled by two reviewers to summarise the data from the included studies. The spreadsheets will then be combined into one. The overall agreement rate between the two investigators will be calculated using Cohen's  $\kappa$  statistic. Disagreements will be resolved by a third investigator.

### Management of missing data

The investigator will be contacted via email in the case that key study specifics or outcome data are missing. If

a response is not received within 2 weeks, a reminder email will be sent. A further 2 weeks waiting period will be allowed for responses; if no response or connection is established with the investigator, these studies will be excluded from the analysis.

### Data management

Data management will be the responsibility of investigators. A Google Drive folder with shared access among the investigators will be provided for the systematic review which will encompass the protocol, manuscripts and supplementary files from included and excluded studies, as well as documentation of steps in data extraction and analysis, risk of bias and quality assessment. A back-up of the records will be stored on a second hard drive. EndNote V.X9 reference management software will be used in the study.

### Outcomes

The primary outcome is the mean difference in systemic inflammatory markers and the secondary outcome is the change in lipid profile between study arms at the end of the statin intervention. The outcomes of the systematic review will be classified into primary and secondary outcomes as follows:

1. Systemic inflammatory markers: Data will be provided as a change in percent over time for hsCRP, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, sCD14 or sCD16.
2. Lipid profile: Data will be provided as a change in percent over time for total cholesterol, LDL, high-density lipoprotein and triglycerides.

## ANALYSIS

### Descriptive analysis

Studies will be categorised by each type of statin intervention and comparison, with data tabulated in narrative form to illustrate the study populations, interventions, durations and outcomes. The outcomes from included studies will provide the following:

1. Type of intervention (statin) and sample size.
2. Intervention outcomes will include the change in lipid profile and other inflammatory biomarkers such as hsCRP, CRP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, sCD14 or sCD16.

The outcomes will be analysed together using the Cochrane Review Manager V.5.3 software, according to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. If statistical heterogeneity is detected, the random-effects model will be adopted. In terms of considerable statistical heterogeneity, a qualitative summary will be provided by a table, as described above. This will be done by the lead investigator in liaison with a second investigator for accuracy.

### Statistical analysis

We will analyse dichotomous data as risk ratios or ORs with 95% CIs and continuous data as mean differences or standardised mean differences. We will perform meta-analyses only if the treatment participants (age group),

the underlying clinical question (disease type) and outcomes (assessed inflammatory markers) are similar enough. If an RCT consists of multiple arms, we will include only the relevant arms. A meta-analysis on LDL-C will be performed to assess the potency of statins; for each study, this will be reported as standardised mean differences with its 95% CI. A scatter plot of the percentage change in LDL-C against percentage change in inflammatory biomarkers over a specific time period will be performed to assess the correlation between lipid profile and inflammation. Heterogeneity and potential sources of heterogeneity will be assessed and quantified using  $I^2$  and  $Q$  statistics. Funnel plot and Egger's test will be used to assess publication and small sample size bias. Subgroup analysis of identified studies will be stratified based on statin type, concentration and intervention period. Univariable and multivariable meta-regression analysis will be used to investigate the potential sources of heterogeneities. Potential outliers will be investigated in a sensitivity analysis by dropping each study at a time. The Duval and Tweedie trim-and-fill will be used to adjust estimates for the effects of publication bias, if any.

This systematic review will provide further insight into the effectiveness of statins to reduce systemic inflammation in various stages of chronic disease conditions, inform on the most potent statin to reduce systemic inflammation and optimal dosing. In addition, this study will add and improve the existing knowledge of the effects of statins on inflammatory markers and may further provide a basis for future clinical trials in specific diseases.

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**Contributors** RG and FT conceived and planned the idea. BM, SS and MO designed the study protocol. SS and BM designed the figure and wrote the first draft. RG, FT and MO revised the protocol. APK and DB provided valuable insight into data acquisition and statistical analysis. DB and RW revised and designed the reporting

of literature. SM, KS, EN, GG and CS critically reviewed the protocol. All authors have approved and contributed to the final written manuscript.

**Funding** This publication was produced by StatinTB which is part of the EDCTP2 programme supported by the European Union (grant number RIA2017T-2004-StatinTB). RJW is supported by the Francis Crick Institute which is funded by Wellcome (FC0010218); Medical Research Council (FC0010218) and Cancer Research UK (FC0010218). RJW also receives support from Wellcome (104803, 203135). The work was supported by the Wellcome Trust CIDRI-Africa 203135Z/16/Z fund.

**Disclaimer** The views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP and Wellcome Trust.

**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.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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