BMJ Open

Examining anti-inflammatory therapies in the prevention of cardiovascular events: protocol for a systematic review and network meta-analysis of randomised controlled trials

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To cite: Boczar KE, Shin S, Bezzina KA, *et al*. Examining anti-inflammatory therapies in the prevention of cardiovascular events: protocol for a systematic review and network meta-analysis of randomised controlled trials. *BMJ Open* 2022;**12**:e062702. doi:10.1136/bmjopen-2022-062702

► 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-2022-062702).

Received 09 March 2022
Accepted 07 June 2022

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ABSTRACT

Introduction Inflammation is emerging as an important risk factor for atherosclerotic cardiovascular disease and has been a recent target for many novel therapeutic agents. However, comparative evidence regarding efficacy of these anti-inflammatory treatment options is currently lacking.

Methods and analysis This systematic review will include randomised controlled trials evaluating the effect of anti-inflammatory agents on cardiovascular outcomes in patients with known cardiovascular disease. Studies will be retrieved from Medline, Embase, the Cochrane Central Register of Controlled Trials, as well as clinical trial registry websites, Europe PMC and conference abstract handsearching. No publication date or language restrictions will be imposed. Eligible interventions must have some component of anti-inflammatory agent. These include (but are not limited to): non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, prednisone, methotrexate, canakinumab, pexelizumab, anakinra, succinobucol, losmapimod, inclacumab, atreleuton, LP-PLA$_2$ (darapladib) and sPLA$_2$ (varespladib). The primary outcomes will include major adverse cardiac events (MACE), and each individual component of MACE (myocardial infarction, stroke and cardiovascular death). Key secondary outcomes will include unstable angina, heart failure, all-cause mortality, cardiac arrest and revascularisation. Screening, inclusion, data extraction and quality assessment will be performed independently by two reviewers. Network meta-analysis based on the random effects model will be conducted to compare treatment effects both directly and indirectly. The quality of the evidence will be assessed with appropriate tools including the Grading of Recommendations, Assessment, Development and Evaluation profiler or Confidence in Network Meta-Analysis tool.

Ethics and dissemination Ethics approval is not required for this systematic review. The findings will be disseminated through a peer-reviewed journal.

PROSPERO registration number CRD42022303289.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Analysis of data within the structure of a network meta-analysis allows for the direct and indirect comparison of anti-inflammatory medications for atherosclerotic cardiovascular disease.
⇒ A rigorous search of published and unpublished data will be conducted.
⇒ Article selection process, data extraction and risk of bias will all be performed by two reviewers in parallel.
⇒ Quality of evidence across the included studies will be assessed and summarised.
⇒ Potential limitations include residual confounding factors biasing results.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of mortality and morbidity around the world.[1 2] The incidence of myocardial infarctions (MI) has been dramatically lowered in populations that have pursued a strategy of aggressive detection and control of traditional cardiovascular risk factors for coronary artery disease (CAD), like hypertension, diabetes, cigarette smoking and elevated low-density lipoprotein cholesterol (LDL-C).[2]

Despite adopting a strategy of aggressively controlling traditional risk factors for CVD, major adverse cardiovascular events (MACE) unfortunately continue to occur at high rates.[3] Thus, much attention is now focused on other potentially modifiable risk factors that can be targeted to further reduce the burden of ASCVD.

The pathogenic basis of atherosclerosis is a complex process; we now know that its biological basis is more intricate than simply attributing it to intimal infiltration of LDL-C. Thus, we are beginning to acknowledge that our therapies will need to extend beyond treatment for the traditional risk factors. In

particular, recent clinical and experimental evidence has supported inflammation as playing a key role in the initiation, progression and eventual overt clinical manifestations of ASCVD.[4]

Contribution of inflammation in the pathophysiology of atherosclerosis

ASCVD is now thought of as a chronic inflammatory disease of the coronary vasculature which is initially triggered by intimal LDL-C infiltration.[2] An early mechanism in the development of clinically manifest CAD is the exposure of the intimal endothelium to harmful stimuli, like hypercholesterolaemia, elevated blood pressure and importantly, inflammation.[2] This impairs its ability to act as a functional barrier and leads to its 'activation'. After their activation, vessel endothelial cells increase their expression of leucocyte adhesion molecules.[2 5 6] This increased expression allows the migration of neutrophils and monocytes into the subendothelial space from the circulating blood.[2] Once inside the vessel wall, these monocytes then differentiate into macrophages and begin to ingest modified LDL-C particles, eventually becoming lipid-laden foam cells.[2] The aggregation of foam cells results in a yellow coloured 'fatty streak' within the arterial wall and thereby the first overt sign of ASCVD.[2]

From a clinical perspective, inflammatory mediators have shown to play a crucial role in mediating thrombotic complications of atherosclerosis, namely MI and ischaemic stroke.[7 8] This fact has spurred the clinical evaluation of inflammation as a therapeutic target in an attempt to further reduce the burden of CVD.[9–12]

Interventions

The encouraging results obtained from basic CVD research endorsed the early translation of anti-inflammatory agents into the clinical setting, which unfortunately failed on several early investigations.[13 14] However, since these early clinical trials, there have also been a multitude of successes, and there is a plethora of new research looking at various anti-inflammatory therapies for the mitigation of cardiovascular events.

While these randomised controlled trials (RCTs) have primarily compared these novel anti-inflammatory agents to placebo (and background of statin therapy), few, if any, have been compared with other anti-inflammatory therapies. Thus, there is currently a paucity of literature regarding the relative effectiveness of these therapies.

This review will provide a contemporary investigation of the relative efficacy of various anti-inflammatory medications for the prevention of MACE. The study is unique in that it will compare a comprehensive list of anti-inflammatory therapies not just with placebo, but with other anti-inflammatory interventions using network meta-analysis (NMA). Additionally, our review will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) recommendations.[15]

Objectives

The primary objective of our systematic review and NMA is to assess the relative effectiveness of anti-inflammatory therapies in cardiac disease, examined in RCTs. Our results will strengthen the understanding of the benefit of each individual anti-inflammatory therapy, and will also allow the comparison of the relative effects of each intervention.

METHODS AND ANALYSIS

This protocol was developed according to the PRISMA-P 2015 checklist[15] (see online supplemental file 1). Important amendments made to the protocol will be documented and published alongside the results of the systematic review.

Types of studies

RCTs will be included in this study.

Population

Our systematic review will include all patients with known CAD, regardless of age or sex. Additionally, participants with both acute coronary syndromes (ACS) as well as stable CAD will be included. However, if significant subgroup differences are discovered between interventions used to treat those with ACS versus those with stable CAD, we will conduct a subgroup analysis to further explore this heterogeneity.

Intervention

Eligible interventions must have some component of anti-inflammatory agent. We will include any anti-inflammatory medication, including (but not limited to): non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, prednisone, methotrexate, canakinumab, pexelizumab, anakinra, succinobucol, losmapimod, inclacumab, atreleuton, LP-PLA$_2$ (darapladib) and sPLA$_2$ (Varespladib). We will not consider any medication which does not have a primary mechanism of action via the inhibition of inflammation (eg, statins or allopurinol).

Comparisons

All medications with a primary mechanism of action that targets the inflammatory pathway will be included in this systematic review. Treatment arms will be considered regardless of whether they received any other type of control or experimental intervention.

Primary outcome

The following primary outcome will be extracted:

- MACE and each individual component of MACE:
  - MI.
  - Stroke.
  - Cardiovascular death.

We will extract secondary outcomes and adverse outcomes from the studies that meet the inclusion criteria.

Key secondary outcomes

- Unstable angina.
- Heart failure.
- All-cause mortality.
- Cardiac arrest.
- Revascularisation.

Key adverse outcomes

These relate to adverse events suggested in previous trials and include, but are not limited to:

- Infection/pneumonia.
- Diarrhoea/GI upset.
- Malignancy.

Years of publication considered

There will be no limitations on the year of publication of studies.

Language

There will be no restriction based on language of the publication. If a potential study is identified that is not written in English, we will use translational services if possible.

Study publication status

We will include both published and unpublished studies in our systematic review. We will search for ongoing studies in the Clinicaltrials.gov and WHO's International Clinical Trials Registry Platform (ICTRP) and will consider these for inclusion when relevant.

Search strategy

The search strategy will be developed by a medical librarian (SV) in collaboration with team members using a combination of subject headings and keywords in Medline; it will then be peer-reviewed by a second librarian as per PRESS guidelines.[16] It will then be run in the various databases listed below from inception. Search results will be exported to Covidence and duplicates will be eliminated using the platform's duplication identification feature. We will rerun our search prior to the final analysis. A draft of the Medline search strategy is included in online supplemental file 2.

Filters

Cochrane RCT search filters will be employed for both Medline and Embase.[17]

Information sources

We will conduct searches of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL).

If there is missing information that is not reported, we will contact study authors by email to obtain more information. If no replies from authors are received, we will send two subsequent emails at 2 and 4 weeks.

We will search reference lists of identified studies by hand to identify additional possible relevant literature.

Grey literature will be searched to identify potential relevant research that has not been published. These sources include:

- Clinical trial registries:
  - ClinicalTrials.gov
  - WHO's ICTRP.
- Preprints from Europe PubMed Central (PMC).
- Conference abstracts will be included as part of the Embase database search. Gaps in Embase indexation will be addressed with hand searching of select relevant conferences:
  - American Cardiology Conference.
  - American Heart Association Conference.
  - European Society of Cardiology Conference.
  - Canadian Cardiovascular Congress.

If RCTs are registered but have not been published at the time of our search, they will be screened and will be included in the analysis if they are eligible and sufficient information is available.

Selection process

COVIDENCE software will be used for study screening. Following duplication removal, study screening and selection will be conducted by two independent reviewers in parallel (KEB, KAB, ShS, ALP, AG and SaS), based on the prespecified inclusion and exclusion criteria.

The first stage of identifying potentially eligible studies will be conducted by screening titles and abstracts in COVIDENCE. When disagreements between two reviewers occur, discussion and consensus will be used to resolve the conflict. When agreement cannot be reached, a third reviewer (KAB) will ultimately resolve the disagreement. Once the first round of screening by titles and abstracts is completed, eligible studies will undergo a full text review by the two reviewers independently (KEB, KAB, ShS, ALP, AG and SaS) according to the process outlined above.

We will track and report reasons for exclusion in a PRISMA flow diagram. If there are multiple reports of the same study that are identified, we will be consider them together.

Data extraction and management

For data collection, a predesigned, standardised data extraction sheet will be used. The reviewers will first test the extraction sheet on five studies. We will then discuss and make amendments to the extraction sheet as necessary. Finally, the data extraction process as well as risk of bias assessment of all included studies will be performed in parallel by two independent reviewers (KEB, KAB, ShS, ALP, AG and SaS). Information pertaining to anti-inflammatory medication characteristics (type of anti-inflammatory, length of therapy, dose), participant characteristics, comparators, setting, lost to follow-up and clinical outcomes will be included in the extraction process.

We will preferentially extract unadjusted results over adjusted results, if available, to improve consistency.

Data items

Participants

Participant characteristics that are deemed to potentially modify treatment effects from the anti-inflammatory agents will be recorded. Patient characteristics of interest include age, sex, comorbidities (including presence of other inflammatory conditions) and concomitant alternative anti-inflammatory medication use. We will also record the number of participants that were included at baseline in each study, and the number of participants lost to follow-up.

Intervention

We will extract information such as treatment length, length of follow-up, and length of time from acute coronary syndrome (ACS) (if relevant), which could potentially modify the anti-inflammatory treatment effect.

Comparator

We will extract data on the type of comparator used, including dose and duration, as well as baseline demographic data regarding the comparator group participants.

Risk of bias in individual studies

The risk of bias of each included study will be assessed independently by two reviewers (KEB, ShS, ALP, AG and SaS) using the updated Cochrane Collaboration's Risk of Bias (RoB 2) Assessment Tool.[18] Disagreements will be resolved through discussion, and if needed a third reviewer (KAB) will settle any disputes.

The RoB 2 Assessment Tool assesses potential sources of bias in five domains including the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selective reporting. We will evaluate each category as being at 'low risk' of bias, 'high risk' of bias or having 'some concerns' for bias. Finally, we will then give an overall judgement of the trial regarding the risk of bias, with studies again being scored as being at 'low risk' of bias, 'high risk' of bias or having 'some concerns' regarding risk of bias.

Randomisation process

We will assess the randomisation and allocation methods to determine the potential for bias to be introduced due to the creation of groups with important underlying baseline differences.

Deviations from the intended interventions

We will assess whether the effect of assignment to intervention and the effect of adherence to intervention could act as potential sources of bias. This includes assessing whether the participant allocation process was concealed, whether both participants and personnel were blinded when participants were allocated to treatment groups, and whether outcome assessors were also blinded to participant assignment. We will also assess whether deviations from the intended intervention were balanced between groups, and whether failure to adhere to the intended intervention could influence the outcomes.

Missing outcome data

We will assess whether outcome data was available for all randomised participants, and if not, whether the missingness could influence the results.

Measurement of the outcome

We will assess whether the method of measuring the outcome was appropriate, and whether the ascertainment of the outcome could have differed between intervention groups.

Selective outcome reporting

We will look for evidence that the authors omitted reporting relevant outcomes, or that data were not evaluated in accordance with a prespecified analysis plan.

Summary measures of treatment effect

Dichotomous outcomes will be presented as either ORs or risk ratios and reported with 95% CIs.

Data synthesis

Clinical heterogeneity will be explored by examining the variation in several patient and study characteristics including population baseline participant demographic variables, the use and composition of 'optimal medical therapy', study outcome definitions and other relevant study characteristics.

Network meta-analysis

If we identify that at least two studies are clinically homogeneous, then we will perform a meta-analysis. Our results will be analysed using an NMA.[19] An NMA uses an interconnected network of treatments, which thereby allows for the assessment of the relative efficacy of these treatments for a particular medical indication.[20] Both direct and indirect comparisons can be made within the network, so long as all trials included in the analysis are contained within the network.[21–23] For our NMA, we will create a model which compares anti-inflammatory interventions for ASCVD.

Data analysis

We will perform our statistical analyses in a Bayesian framework using the OpenBUGS software.[24] To address statistical heterogeneity, we will use random effects models. We will assess the fit of each model to the data by using the posterior mean residual deviance. We will then compare the models by using the Deviance information criterion.[25] Satisfying the consistency assumption is critical in the validation of an NMA, in part to ensure that included studies are comparable within the network. We will assess the validity of this assumption by reviewing the patient inclusion and exclusion criteria for each study included in the summary analysis, to ensure that the patient and study characteristics are sufficiently similar.

If quantitative data analysis is not appropriate, a qualitative description and table of the included studies and data will be performed and displayed.

Subgroup analysis

Several prespecified subgroup analyses will be conducted if data permits. These include:

- Sex.
- Setting of ASCVD (ACS vs non-ACS setting).
- Time after index event for initiation of anti-inflammatory agent.
- Published vs unpublished literature.

Assessment of reporting biases

To assess for small-study effects we will include the total number of patients in the study as a covariate in our meta-regression analysis. We will also create funnel plots[26] to evaluate for potential reporting bias.

Sensitivity analyses

We will perform an additional analysis whereby we exclude studies which are deemed to be at either 'high risk' or to have 'some concerns' of bias on the Cochrane RoB 2 Assessment Tool.[18]

We will also conduct additional analyses with fixed-effects models for the pairwise and NMA.

Confidence in cumulative evidence

The quality of the evidence across included studies will be summarised with an appropriate tool,[27]with possible tools including the Grading of Recommendations, Assessment, Development,and Evaluation profiler[28] or Confidence in Network Meta-Analysis tool.[29]

Patient and public involvement

There is no patient or public involvement in this study.

ETHICS AND DISSEMINATION

We did not require ethics approval for this systematic review and NMA. The findings will be disseminated through a peer-reviewed journal.

DISCUSSION

This systematic review and NMA will address questions regarding the comparative effectiveness of anti-inflammatory therapies for the treatment of ASCVD. This topic is important for several reasons. As mentioned, ASCVD is an extremely common problem, and is a leading cause of morbidity and mortality.[1 2] With a growing number of therapeutic agents being developed to target the inflammation pathway, it is extremely useful for practitioners to have knowledge regarding the relative comparison of these novel drugs. Thus, this study could be important for clinical practice, providing information regarding relative benefits and harms from these anti-inflammatory agents. Furthermore, with the burden of the potential financial cost of these drugs for healthcare payers, this review will be potentially useful regarding funding decisions.

The major strength of this systematic review and NMA is that it will comprehensively summarise the evidence regarding anti-inflammatory benefit and harm for the treatment of ASCVD. Moreover, this NMA will allow both direct and indirect comparison between these novel anti-inflammatory medications. Additionally, our comprehensive search strategy will attempt to discover both published and unpublished (grey) literature in the field. Potential limitations include the possibility of residual confounding influencing our results. The strength of our review will be dependent on the existing evidence base for this topic area. If only one or two RCTs exist for a given comparison in the network, then the strength of the analysis will reflect that. The sample size and the number of included studies may be small due to the novelty and resource-intensive nature of conducting an RCT of this nature on this topic.

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Acknowledgements We thank Becky Skidmore, MLS, Ottawa, ON, for peer review of the MEDLINE search strategy.

Contributors Conceptualisation: KEB and GAW; Methodology: KEB, SV, RB and GAW; Project administration: KEB; supervision: GAW and RB; writing—original draft: KEB; writing—review and editing: KEB, ShS, ALP, AG, SaS, KAB, CAF, SV, RB and GAW. KEB is the guarantor of the review.

Funding KEB holds a Canadian Institutes of Health Research Fellowship (FRN: 171284). Otherwise, this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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.

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Protocol for a systematic review and network meta-analysis of randomised controlled trials examining anti-inflammatory therapies in the prevention of cardiovascular events

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Online Supplemental: PRISMA-P 2015 Checklist

This checklist has been adapted from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		Abstract
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		Title
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		Contributors
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		X	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	X		Funding
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		Contributors, Funding
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		Introduction

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		Methods
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		Methods
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		Methods
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	X		Appendix
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		Methods
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		Methods
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		Methods
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		Methods
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		Methods
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	X		Methods
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		Methods
	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 (e.g., I^2, Kendall's tau)	X		Methods
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		Methods
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		Methods

Section/topic	#	Checklist item	Information reported		Section
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		Methods
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		Methods

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Online Supplemental: Search Strategies

Table 1. Medline Search

#	Searches
1	exp Arteriosclerosis/ or Plaque, Atherosclerotic/
2	(atherosclero* or athero-sclero* or arteriosclero* or arterial-sclero* or arteriolosclero* or arteriolo-sclero* or vascular sclero* or ASCVD or ASCAD or intima plaque).ti,ab,kf,kw.
3	Acute Coronary Syndrome/ or exp Coronary Disease/
4	((coronary adj3 (arter* or stenos* or disease? or disorder? or syndrom?)) or CAD or SCAD).ti,ab,kf,kw.
5	exp Percutaneous Coronary Intervention/ or exp Myocardial Revascularization/
6	(((aortocoronary or aorto-coronary or coronary) adj3 bypass*) or CABG).ti,ab,kf,kw.
7	exp endarterectomy/ or exp thrombectomy/ or exp Atherectomy/ or exp Embolectomy/
8	(angioplast* or atherectom* or endarterectom* or thrombectom* or thromboendarterectom* or thrombo-endarterectom* or PCI or PTCA or (Percutaneous adj3 (intervent* or revascular*))).ti,ab,kf,kw.
9	or/1-8
10	exp Anti-Inflammatory Agents, Non-Steroidal/
11	(((non-steroidal or nonsteroidal) adj2 (anti-inflammatory or antiinflammatory or analg?esic*)) or NSAID*).ti,ab,kf,kw.
12	(acalabrutinib* or aceclofenac* or acemetacin* or acetaminosalol* or acetylsalicylate* or acetylsalicylic* or aclantate* or actarit* or adalimumab* or afasevikumab* or afimetoran* or alclofenac* or aldafermin* or alminoprofen* or aloxiprin* or amfenac* or aminophenazone* or aminosalicylic* or amlitelimab* or amlodipine* or ampiroxicam* or amtolmetin guacil* or anirolac* or antiflammin* or apadenoson* or apremilast* or araprofen* or ascription* or asivatrep* or astegolimab* or atibuclimab* or atliprofen* or aviptadil* or azathioprine* or azelaic acid* or bakeprofen* or balsalazide* or bardoxolone* or bardoxolone methyl* or belumosudil* or bendazac* or benorilate* or benoxaprofen* or bermoprofen* or bimosiamose* or brazikumab* or brensocatib* or brimonidine* or bromfenac* or broperamole* or bucloxic acid* or bucolome* or bufexamac* or butibufen* or camobucol* or carbasalate* or carotegrast* or carprofen* or cedirogant* or celecoxib* or cibinetide* or cicloprofen* or cimicoxib* or cinmetacin* or cinnoxicam* or clidanac* or clofezone* or clonixin* or clonixin lysine* or cloximate* or crisaborole*).ti,ab,kf,kw.

13	(dagrocorat* or danicopan* or dapansutrile* or dapatifagene navolactibac* or darbufelone* or daxdilimab* or dazodalibep* or dehydrozingerone* or demethoxycurcumin* or deracoxib* or deucravacitinib* or dexibuprofen* or dexketoprofen* or dexpemedolac* or diclofenac* or didemethoxycurcumin* or diflunisal* or diftalone* or dimethyl fumarate* or dimethyl sulfoxide* or diphenpyramide* or ditazole* or droxicam* or duometacin* or ebdarokimab* or ebselen* or edasalonexent* or efruxifermin* or elsibucol* or emavusertib* or emorfazone* or emvododstat* or endolac* or enfenamic acid* or enflicoxib* or enpatoran* or epirizole* or etodolac* or etofenamate* or etoricoxib* or evobrutinib* or felbinac* or fenamic acid* or fenbufen* or fenclofenac* or fenclozic acid* or fendosal* or fenflumizole* or fenoprofen* or fentiazac* or fepradinol* or feprazone* or firategrast* or firocoxib* or flobufen* or flosulide* or flufenamate aluminum* or flufenamic acid* or flunixin* or flunoxaprofen* or fluproquazone* or flurbiprofen* or flutiazin* or fosdagrocorat* or fosfosal* or furaprofen* or furcloprofen* or furobufen* or furofenac* or fuzapladib*).ti,ab,kf,kw.
14	(glucametacin* or gluconate zinc* or guacetisal* or guaimesal* or gusacitinib* or hydroxychloroquine* or ibrigampar* or ibufenac* or ibuprofen* or ibuproxam* or icoduline* or icosapentaenoic acid* or iguratimod* or ilonidap* or imidazole salicylate* or imisopasem manganese* or imsidolimab* or incyclinide* or indameth* or indometacin* or indoprofen* or ipsalazide* or iptacopan* or isecarosmab* or isofezolac* or isonixin* or isoxepac* or isoxicam* or itepekimab* or kebuzone* or ketoprofen* or ketoprofen lysine* or ketorolac* or lazertinib* or lazucirnon* or leflunomide* or lenabasum* or licofelone* or lifitegrast* or lirentelimab* or lobuprofen* or lonazolac* or lorecivivint* or lornoxicam* or losmiprofen* or loxoprofen* or lumiracoxib* or lusvertikimab* or lyprinol* or lysine acetylsalicylate*).ti,ab,kf,kw.
15	(mabuprofen* or magnesium salicylate* or manoalide* or mapracorat* or mavacoxib* or meclofenam* or mefenamic acid* or meloxicam* or melrilimab* or mesalazine* or methotrexate* or metiazinic acid* or metoxibutropate* or milategrast* or mipragoside* or mirococept* or miroprofen* or mivavotinib* or mofebutazone* or mofezolac* or mongersen* or morazone* or morniflumate* or mosedipimod* or nabumetone* or nangibotide* or naproxcinod* or naproxen* or navamepent* or nepafenac* or neurofenac* or neurotropin* or nictindole* or niflumic acid* or nimesulide* or ocarocoxib* or odalprofen* or olsalazine* or ordesekimab* or ormeloxifene* or orpanoxin* or otenaproxesul* or oxaceprol* or oxametacin* or oxaprazine* or oxaprozin* or oxicam derivative* or oxindanac* or oxyphenbutazone*).ti,ab,kf,kw.
16	(palifermin* or parcetasal* or parecoxib* or pelubiprofen* or pemedolac* or perisoxal* or phenylbutazone* or phenylbutazone megallate* or picolamine salicylate* or piketoprofen* or pimeprofen* or pipebuzone* or piproxen* or pirazolac* or pirfenidone* or piroxicam* or piroxicam beta cyclodextrin* or pirprofen* or plonmarlimab* or plozalizumab* or polmacoxib* or pralnacasan* or pranoprofen* or prinomide* or prinomide triethanolamine* or proglumetacin* or proquazone* or pyrazinobutazone* or quellor* or rapamycin* or rasagiline* or ravagalimab* or relfovetmab* or reltecimod* or remestemcel L* or resatorvid* or rimacalib* or rimazolium* or risankizumab* or robenacoxib* or rofecoxib* or romazarit* or rosiptor* or rosmarinic acid* or rovazolac* or rozibafusp alfa* or ruxolitinib* or salazosulfapyridine* or salicylic acid* or salnacedin* or salsalate* or satralizumab* or scalaradial* or semapimod* or semorinemab* or sibofimloc* or simufilam* or sudoxicam* or sulfosalicylate samarium* or sulindac* or suprofen* or suxibuzone*).ti,ab,kf,kw.
17	(talniflumate* or tapinarof* or tazofelone* or telazorlimab* or tenidap* or tenosal* or tenosiprol* or tenoxicam* or tepoxalin* or teriflunomide* or tesnatilimab* or tiaprofenic acid* or tiaramide* or tilmacoxib* or tilnoprofen arbamel* or tilomisole* or timegadine* or tioxamast* or

	tioxaprofen* or tirnovetmab* or tolebrutinib* or tolfenamic acid* or tolmetin* or tomaralimab* or tomicorat* or torudokimab* or tozorakimab* or tralokinumab* or tribuzone* or triethanolamine salicylate* or tropesin* or tryptamide* or ufenamate* or valategrast* or valdecoxib* or valerylsalicylic acid* or vasoactive intestinal polypeptide* or vedaprofen* or velsecorat* or vemircopan* or verramed* or vilobelimab* or vixarelimab* or ximoprofen* or zabedosertib* or zaloglanstat* or zaltoprofen* or zaurategrast* or zidometacin* or zinc salicylate* or zoliprofen* or zomepirac*).ti,ab,kf,kw.
18	exp Colchicine/
19	(Colbenemid* or Colchichin* or colchicum* or colchily* or colchineos* or colchimedio* or colchiquim* or colchisol* or colchysat* or colcin* or colcrys* or colctab* or colgout* or colrefuz* or colsaloid* or Condylon* or gloperba* or goutichine* or goutnil* or kolkicin* or kolkisin* or mitigare* or tolchicine*).ti,ab,kf,kw.
20	(64-86-8* or SML2Y3J35T*).rn.
21	Prednisone/
22	(adasone* or acsis* or ancortone* apo-prednisone* or bicortone* or biocortone* or cartancyl* or colisone* or Cortan* or cortancyl* or cortidelt* or cortiprex* or cotone* or cutason* or dacorten* or dacortin* or decortancyl* or decortin* or de-cortisyl* or decortisyl* or dihydrocortisone* or dihydrocortisone* or dekortin or dellacort* or deltacorten* or delta-cortelan* or delta-cortisone* or deltacortisone* or deltacortone* or delta-dome* or delta-prenovis* or deltasone* or delitisone* or deltison* or deltra* or diadreson* or di-adreson* or drazone* or econosone* or encorton* or encortone* or enkorton* or enkortolon* or fernisone* or fiasone* or hostacortin* or insone* or incocortyl* or juvason* or kortancyl* or liquid pred* or lodotra* or lodtra* or lisacort* or me-korti* or meprison* or metacortandracin* or Meticorten* or meticortine* or nisona* or nizon* or novoprednisone* or nurison* or Orasone* or orisane* or panafcort* or paracort* or panasol* or parmenison* or pehacort* or predeltin* or precort* or precortal* or prednicen* or prednicorm* or prednicort* or prednicot* or predni tablinen* or prednidib* or prednilonga* or predniment* or prednison* or prednitone* or prednizon* or prednovister* or presone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or rectrocortine* or servisone* or sone$2 or steerometz* or sterapred* or supercortil* or ultracorten* or urtilone* or winpred* or wojtab* or zenadrid*).ti,ab,kf,kw.
23	(53-03-2 or VB0R961HZT).rn.
24	Methotrexate/
25	(abitextrate* or abitrexate* or amethopterin* or amethopterine* or ametopterine* or antifolan* or biotrexate* or brimexate* or canceren* or emtexate* or emthexat* or emthexate* or emtrexate* or enthexate* or farmitrexat* or farmotrex* or fauldexato* or folex* or ifamet* or imeth$2 or intradose MTX or jylamvo* or lantarel* or ledertrexate* or lumexon* or maxtrex* or medsatrexate* or metatrexan* or metex* or methoblastin* or methohexate* or methotrate* or methotrexat* or methylaminopterin* or metical* or metoject* or metotressato* or metothrexate* or metotrexat* or metotrexin* or metrex* or metrotex* or mexate* or neotrexate* or nordimet* or novatrex* or otrexup* or rasuvo* or reditrex* or reumatrex* or rheumatrex* or texate* or texorate* or tremetex* or trexall* or trexeron* or trixilem* or xaken* or xatmep* or zexate*).ti,ab,kf,kw.
26	(59-05-2 or YL5FZ2Y5U1).rn.
27	Interleukin-1beta/
28	(ACZ-885* or ACZ885* or Canakinumab* or ilaris*).ti,ab,kf,kw.
29	(914613-48-2 or 37CQ2C7X93).rn.

30	Antibodies, Monoclonal, Humanized/
31	(pexelizumab or "h5G1.1-SC*").ti,ab,kf,kw.
32	(219685-93-5 or CHZ6OLQ3UU).rn.
33	Interleukin 1 Receptor Antagonist Protein/
34	(Anakinra* or Antril* or Kineret* or il-1ra* or (interleukin 1 receptor adj1 (antagonist or block* or inhibit*))).ti,ab,kf,kw.
35	(143090-92-0 or 9013DUQ28K).rn.
36	(agi-1067* or agi1067* or agz-1067* or agz1067* or probucol succinate* or Succinobucol*).ti,ab,kf,kw.
37	(216167-82-7 or J1J54V24R4).rn.
38	(ftx-1821* or ftx1821* or gsk-856553* or gsk856553* or gw-856553* or gw856553* or Losmapimod* or sb-856553* or sb856553*).ti,ab,kf,kw.
39	(F2DQF16BXE or 585543-15-3).rn.
40	(lc1004* or lc-1004* or inclacumab* or ro4905417* or ro-4905417*).ti,ab,kf,kw.
41	(1256258-86-2 or A6734I702L).rn.
42	(Atreleuton* or a85761* or a-85761* or abt761* or abt-761* or via-2291* or via2291*).ti,ab,kf,kw.
43	(U301T88E1M or 154355-76-7).rn.
44	(darapladib* or sb-480848* or sb480848*).ti,ab,kf,kw.
45	(356057-34-6 or UI1U1MYH09).rn.
46	(Varespladib* or Varepladib* or ly315920* or ly-315920* or s-5920* or s5920*).ti,ab,kf,kw.
47	(2Q3P98DATH or 172732-68-2).rn.
48	or/10-47
49	randomized controlled trial.pt.
50	controlled clinical trial.pt.
51	randomized.ab.
52	placebo.ab.
53	clinical trials as topic.sh.
54	randomly.ab.
55	trial.ti.
56	49 or 50 or 51 or 52 or 53 or 54 or 55
57	exp animals/ not humans.sh.
58	56 not 57
59	9 and 48 and 58