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Patients' and general practitioners' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies

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TITLE

Patients' and general practitioners' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies

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KEYWORDS

systematic review; qualitative research; cardiovascular disease; attitudes; perceptions; drug initiation; statins; antihypertensive drugs; primary prevention

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ABSTRACT

Introduction: Lipid lowering drugs and antihypertensive agents can be prescribed for the primary prevention of cardiovascular disease. In some cases, eligible patients are not started on preventive drugs. We aim to systematically review qualitative studies assessing general practitioners' and patients' attitudes and perceptions towards drug initiation for primary prevention of cardiovascular disease.

Methods and analysis: MEDLINE, MEDLINE In Process, EMBASE, PsychINFO, CINAHL and Applied Social Sciences Index and Abstracts (ASSIA), Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey will be searched without restrictions on date or language of publication. Searches will be limited to studies of qualitative design, standalone or in the context of a mixed-method design, focusing on cardiovascular drug initiation for primary prevention. The primary outcome is the attitudes of general practitioners and patients towards preventive drug initiation. Two reviewers will independently carry out the study selection, data extraction and quality assessment. The Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist will be used to assess the quality of included studies. The findings will be analysed using thematic synthesis.

Ethics and dissemination: This systematic review does not require ethical approval as primary data will not be collected. The results of the study will be published in a peer-reviewed journal and presented at relevant conferences.

Systematic review registration: PROSPERO CRD42018095346

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review will utilize a systematic approach to summarize qualitative evidence on preventive drug initiation in primary care settings
- It will provide a better understanding of what influences GPs' and patients' decisions regarding initiation of preventive treatment.
- The study will not review studies addressing the initiation of aspirin for the primary prevention of cardiovascular disease.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of deaths worldwide [1]. It accounts for 26% of deaths in the United Kingdom and 31% of deaths globally [1 2]. One of the ways to prevent CVD is through prescribing drugs for primary prevention. National and international guidelines recommend primary preventive treatment for patients at an increased risk of developing a cardiovascular event [3-6]. Patients considered at an increased risk include patients who have a 10-year CVD risk of 10% or more or patients with clinically measured blood pressure of 140/90 mmHg or higher [4 6]. The recommendations are supported by evidence from clinical trials demonstrating the beneficial effects of lipid lowering drugs and antihypertensive agents in the primary prevention of CVD [7-10]. However, studies have reported low prescribing rates of preventive drugs [11-14]. Patients eligible for statins are undertreated [13 14]; one study has reported that 50% of patients with a CVD risk ≥20% were not prescribed statins for primary prevention [14]. In addition, the detection and treatment of hypertension remains low in parts of the world [15 16]. 49% of adults with hypertension aged 35-84 years were treated in Japan compared to 80% in the United States [15]. However, the initiation rate for antihypertensive drugs in younger eligible adults in the United States is suboptimal [17]. A study that explored antihypertensive drug initiation among young adults with regular access to primary care found that only 34% of patients aged 18-39 years were started on antihypertensive drugs compared to 44% of patients aged 40-59 years [17].

The suboptimal prescribing patterns may be a result of GPs' poor adherence to guideline recommendations. A study conducted in German general practices estimated that around 50% of GPs did not adhere to the guidelines [18]. GPs have expressed concerns regarding the evidence the guidelines were based on and whether following the guidelines will allow them to meet their patients' needs [19 20]. Nevertheless, the variation in prescribing patterns indicates that there are patient- and GP-related barriers to initiating primary preventive treatment. Previous research identified GP-related barriers such as concerns about patient adherence to medication, over-medicalization of healthy individuals and side effects [21]. With respect to patient-related barriers, a study reported that patients preferred making lifestyle changes and had concerns about the side effects of taking medication [22]. In

addition, patients' trust in their GP's medical judgment played a role in accepting preventive treatments [22].

We are interested in studies that explore the attitudes of GPs and patients towards initiating treatments for the primary prevention of CVD. A scoping search was carried out to identify existing literature and to estimate the volume of studies available on our topic of interest. The majority of published studies address the issue of adherence to medication or prescribing drugs for secondary prevention [23] [24]. However, the search retrieved a number of qualitative studies that investigate patient and health professional-related factors influencing drug prescribing for primary prevention. The search retrieved a systematic review published in 2012 that assessed qualitative literature about initiating and adhering to preventive drugs for CVD. The review discussed factors associated with initiating preventive medication and reported that initiation was influenced by the health professional-patient relationship and the organizational structure of the clinical environment [25]. The authors focused on starting and adhering to preventive medication with no differentiation between primary and secondary prevention. In addition, studies were excluded from the review based on quality assessment. Our review will consider all primary studies addressing our topic of interest regardless of quality to capture all available evidence regarding prescribing cardiovascular drugs for primary prevention. Furthermore, the search retrieved one recently published systematic review that explored patients' attitudes towards taking statins. However, the review did not explore the attitudes of GPs towards statins and was restricted to studies in the English language [26]. The authors explored attitudes only towards statin uptake without differentiating between primary and secondary prevention. The reasons behind taking statins might be different in patients who had a CVD event and patients who are yet to experience a CVD event. Our review will explore a wider range of cardiovascular preventive drugs. We will focus on the uptake of such drugs for primary prevention because initiating therapy in relatively asymptomatic patients can be challenging for both the health professional and the patient and attitudes relating to this preventive approach needs to be identified for successful primary care preventive prescribing. Both reviews did not explore grey literature. Our review aims to explore grey literature databases to maximize the chances of capturing relevant studies.

The decision-making process involved in initiating preventive treatments is complex and influenced by multiple factors that relate to both the GP and the patient. Thus, an up-to-date, methodologically robust systematic review aiming to identify the attitudes and perceptions of GPs and patients towards the initiation of preventive drugs for the primary prevention of CVD is warranted.

Objectives

- Explore GPs' and nurse practitioners' attitudes and perceptions in relation to initiating preventive drugs for primary prevention of CVD in primary care settings.
- Explore patients' attitudes and perceptions towards initiating preventive drugs for primary prevention of CVD in primary care settings.

METHODS AND ANALYSIS

This protocol will use the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to ensure comprehensive reporting of study items [27]. The protocol is registered with PROSPERO (CRD42018095346). The systematic review will follow the reporting guidelines formulated in the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement [28].

Information sources and search strategy

The Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) tool is considered an alternative to PICOS when addressing a qualitative review question and will be used in the proposed systematic review to formulate the search strategy [29]. The search strategy will include a combination of free text words and index terms relating to (drug initiation OR prescription OR decision making) and (attitudes OR experiences OR perceptions OR views OR behaviour) and cardiovascular disease. The formulated search strategy will be applied to MEDLINE database (including MEDLINE In Process) then adapted with necessary adjustments for use in other databases. We will search EMBASE, PsychINFO, CINAHL and

Applied Social Sciences Index and Abstracts (ASSIA) for published studies. In addition, the following grey literature sources will be searched: Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey. The reference lists of included studies will be checked to identify additional eligible studies which were not retrieved by the formulated search strategy. There will be no restriction on date or language of publication. The search will be limited to studies of qualitative design.

Eligibility criteria

Sample

We will include studies of primary care health professionals (GPs and nurse practitioners), in any country, who prescribe cardiovascular preventive drugs. In addition, we will include studies that target patients who are offered a prescription for statins or antihypertensive drugs in a primary care setting. Studies that focus on practitioners or patients involved in the process of decision making or initiation of cardiovascular drugs will be included. Any study that examines practitioners who prescribe preventive drugs and patients who receive such prescriptions for secondary prevention of CVD will be excluded. Studies conducted in secondary care settings will be excluded.

Phenomenon of interest

Studies will be considered for inclusion if they assess patient or practitioner factors associated with the initiation of cardiovascular preventive drugs in primary care settings. Initiation refers to the prescription of preventive drugs by the practitioner and the patient agreeing to take medication for preventive purposes. Therefore, studies that focus on decision making or discuss barriers and facilitators to prescription for primary prevention of CVD will be included. We will exclude studies that focus on adherence and continuation of cardiovascular preventive drugs.

Design / Research type

Our review aims to look at aspects such as attitudes and perceptions. These are best explored through a qualitative approach. Therefore, any qualitative studies, stand alone or in the context of a mixed-method design, focusing on cardiovascular drug prescription for primary prevention will be included. A summary of Sample,

Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) is provided in Table 1.

Table 1. Summary of Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER)

Sample	- General practitioners or nurse practitioners who prescribe statins or antihypertensive drugs. - Patients eligible for cardiovascular preventive drugs or offered a prescription of statin or an antihypertensive drug for primary prevention of cardiovascular disease.
Phenomenon of Interest	The initiation or prescription of statins or antihypertensive drugs.
Design	Studies including qualitative data collection or analysis methods.
Evaluation	Attitudes, perceptions, views or experiences of general practitioners, nurse practitioners or patients related to the initiation of cardiovascular preventive drugs.
Research type	Qualitative and mixed methods studies.

Evaluation

Studies that address the attitudes, perceptions, views or experiences of GPs, nurse practitioners or patients involved in the process of cardiovascular preventive drug initiation will be considered for inclusion. To adhere to the European guidelines, we will include studies that target the prescription of statins or antihypertensive drugs (4-6). We will exclude studies that target the prescription of aspirin as its use for primary prevention is not recommended by several guidelines (5, 27). In addition, studies that assess the attitudes and perceptions of practitioners or patients towards the prescribing of fibrates, niacin, bile acid sequestrants and Omega-3 fatty acid compounds will be excluded as these drugs are not recommended for the primary prevention of CVD [4 5]. In some countries, a polypill that contains a lipid lowering agent and a blood pressure lowering agent is prescribed for CVD risk reduction [30]. Thus, we will consider studies that assess GPs' and patients' attitudes towards polypills.

Selection process

The literature search results will be imported into Endnote X8 (Thomson Reuters, New York), to ensure efficient management of references and to facilitate the study selection process. The process of selecting studies will be carried out in two stages by two independent reviewers. The reviewers will follow explicit inclusion/exclusion criteria to minimize potential bias and to ensure minimal influence of the reviewers' preconceptions. The inclusion/exclusion form is presented in (Appendix 1). The first stage of selection will include screening the titles and abstracts of all identified records against the inclusion criteria. If a study addresses our topic but the abstract lacks sufficient information to assess eligibility for inclusion, the full text will be retrieved to make a definitive decision. In the second stage of selection the two reviewers will retrieve the full texts of included studies and assess them for eligibility. Any disagreements during the selection process will be resolved through discussion. If the two reviewers fail to reach an agreement, a third independent reviewer will be involved for an unbiased decision. The reviewers will keep a record for each article that they have assessed and justify their decision for either inclusion or exclusion. The selection process will be piloted on a small number of studies by the main reviewer to ensure the reliability of the inclusion criteria. The selection process will be illustrated using a PRISMA flow diagram [27].

Data extraction process

An electronic standardised data extraction form will be developed to ensure adequate and consistent extraction of all required information. The form will be piloted using a small number of studies to ensure reliability and validity and adjusted if necessary. The electronic form will be used to record extracted data on study characteristics, participants' details, theoretical approach, data collection methods, data analysis and findings (Appendix 2). Once extraction is completed by the two reviewers, the forms will be reviewed, and any discrepancies will be resolved through discussion. If the two reviewers fail to reach agreement, a third reviewer will be involved.

Critical appraisal

Two independent reviewers will appraise the quality of the included studies using the Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist [31]. The assessment of quality will be based on the study aims, methodology, study design, sample recruitment, reflexivity, data collection, data analysis, findings, value of research and ethics. The reviewers will keep a record of the quality assessment for each study with an explanation of their decision. Any disagreements will be resolved by discussion or referral to a third independent reviewer. Studies will not be excluded from the review based on quality.

Data synthesis

The NVivo10 software will be used to analyse qualitative data. We will adopt a method of thematic synthesis defined by Thomas and Harden for synthesising qualitative data in systematic reviews [32]. Thematic synthesis includes three stages: First, line by line examination of studies' findings and assigning codes to each line of text based on the meaning and content. Second, codes are then grouped into a hierarchical structure and organized as descriptive themes. Finally, analytical themes will be generated to provide interpretations that surpass the findings of the primary studies and ultimately answer our review question. The thematic synthesis will be carried out by two independent reviewers. The reviewers will discuss the codes and themes with an advisory team and then agree on the analytical stage of thematic synthesis.

Patient and public involvement

This protocol was completed without patient or public involvement. Patients were not invited to contribute to the development of this protocol.

DISCUSSION

The GP's decision to prescribe a preventive drug and the patient's willingness to start treatment for preventive purposes is a multifactorial process. It is essential to understand this process of decision making from a qualitative perspective to enable a more effective approach to cardiovascular disease prevention. This review will summarize the qualitative evidence available on healthcare professionals' and patients' attitudes towards drug initiation. The findings will help us to understand the complex interaction that occurs during the consultation visit between the patient and

their GP and provide evidence to inform healthcare professionals and policy makers regarding barriers and facilitators to primary care cardiovascular preventive prescribing.

ETHICS AND DISSEMINATION

This review will utilize information available from primary studies. Data will not be collected from individuals therefore ethical approval is not required. We aim to disseminate the findings of our review through publication in a peer-reviewed journal and presentation at a relevant conference.

AUTHORS' CONTRIBUTIONS

OQ formulated the research question, performed the scoping search and wrote the first draft. OQ and DB refined research question and search strategy. TM, DB, NA reviewed and revised the draft. All authors read and approved the final manuscript.

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COMPETING INTERESTS

None declared.

REFERENCES

1. World Health Organization. Cardiovascular diseases: Fact sheets 2017 [Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ accessed 1 June 2018.
2. British Heart Foundation. CVD statistics - BHF UK factsheet: British Heart Foundation; 2018 [Available from: https://www.bhf.org.uk/research/heart-statistics accessed 1 June 2018.
3. Boon N, Boyle R, Bradbury K, et al. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100(Suppl 2):ii1-ii67. doi: 10.1136/heartjnl-2014-305693
4. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease London: NICE; 2014 [Available from: https://www.nice.org.uk/guidance/cg181 accessed 1 April 2017.
5. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Atherosclerosis* 2016;252:207-74. doi: 10.1016/j.atherosclerosis.2016.05.037
6. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management London: NICE; 2016 [Available from: https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2 accessed 1 April 2018.
7. Karmali KN, Lloyd-Jones DM, Berendsen MA, et al. Drugs for Primary Prevention of Atherosclerotic Cardiovascular Disease: An Overview of Systematic Reviews. *JAMA cardiology* 2016;1(3):341-9. doi: 10.1001/jamacardio.2016.0218 [published Online First: 2016/07/22]
8. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane database of systematic reviews* 2013(1):Cd004816. doi: 10.1002/14651858.CD004816.pub5 [published Online First: 2013/02/27]
9. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Archives of internal medicine* 2006;166(21):2307-13. doi: 10.1001/archinte.166.21.2307 [published Online First: 2006/11/30]
10. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2016;316(19):2008-24. doi: 10.1001/jama.2015.15629 [published Online First: 2016/11/14]
11. Turner GM, Calvert M, Feltham MG, et al. Under-prescribing of Prevention Drugs and Primary Prevention of Stroke and Transient Ischaemic Attack in UK General Practice: A Retrospective Analysis. *PLoS Medicine* 2016;13(11):e1002169. doi: 10.1371/journal.pmed.1002169
12. Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. *BMC health services research* 2014;14:414. doi: 10.1186/1472-6963-14-414 [published Online First: 2014/09/23]
13. Wu J, Zhu S, Yao GL, et al. Patient Factors Influencing the Prescribing of Lipid Lowering Drugs for Primary Prevention of Cardiovascular Disease in UK General Practice: A National Retrospective Cohort Study. *PLoS ONE* 2013;8(7):e67611. doi: 10.1371/journal.pone.0067611
14. Homer K, Boomla K, Hull S, et al. Statin prescribing for primary prevention of cardiovascular disease: a cross-sectional, observational study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015;65(637):e538-44. doi: 10.3399/bjgp15X686113 [published Online First: 2015/07/28]
15. Ikeda N, Sapienza D, Guerrero R, et al. Control of hypertension with medication: a comparative analysis of national surveys in 20 countries. *Bulletin of the World Health Organization* 2014;92(1):10-19c. doi: 10.2471/blt.13.121954 [published Online First: 2014/01/07]

16. Baker R, Wilson A, Nockels K, et al. Levels of detection of hypertension in primary medical care and interventions to improve detection: a systematic review of the evidence since 2000. *BMJ Open* 2018;8(3):e019965. doi: 10.1136/bmjopen-2017-019965
17. Johnson HM, Thorpe CT, Bartels CM, et al. Antihypertensive Medication Initiation Among Young Adults with Regular Primary Care Use. *Journal of General Internal Medicine* 2014;29(5):723-31. doi: 10.1007/s11606-014-2790-4
18. Oriol-Zerbe C, Abholz HH. Primary prevention of cardiovascular diseases by lipid-lowering treatment in German general practice: results from GPs ignoring guidelines and risk calculators. *The European journal of general practice* 2007;13(1):27-34. doi: 10.1080/13814780601050541 [published Online First: 2007/03/17]
19. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2007;57(545):971-8. doi: 10.3399/096016407782604820 [published Online First: 2008/02/07]
20. Carlsen B, Norheim OF. "What lies beneath it all?" – an interview study of GPs' attitudes to the use of guidelines. *BMC health services research* 2008;8:218-18. doi: 10.1186/1472-6963-8-218
21. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice* 2003;53(494):684-89.
22. Gale NK, Greenfield S, Gill P, et al. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. *BMC Family Practice* 2011;12:59-59. doi: 10.1186/1471-2296-12-59
23. Fung V, Graetz I, Reed M, et al. Patient-reported adherence to statin therapy, barriers to adherence, and perceptions of cardiovascular risk. *PloS one* 2018;13(2):e0191817. doi: 10.1371/journal.pone.0191817
24. Jamison J, Graffy J, Mullis R, et al. Stroke survivors', caregivers' and GPs' attitudes towards a polypill for the secondary prevention of stroke: a qualitative interview study. *BMJ Open* 2016;6(5)
25. Gale N, Marshall T, Bramley G. Starting and staying on preventive medication for cardiovascular disease. *Current Opinion in Cardiology* 2012;27(5):533-41. doi: 10.1097/HCO.0b013e328356dae5
26. Ju A, Hanson CS, Banks E, et al. Patient beliefs and attitudes to taking statins: systematic review of qualitative studies. *British Journal of General Practice* 2018;68(671):e408-e19. doi: 10.3399/bjgp18X696365
27. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *The BMJ* 2009;339:b2700. doi: 10.1136/bmj.b2700
28. Tong A, Flemming K, McInnes E, et al. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Medical Research Methodology* 2012;12:181-81. doi: 10.1186/1471-2288-12-181
29. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qualitative health research* 2012;22(10):1435-43. doi: 10.1177/1049732312452938 [published Online First: 2012/07/26]
30. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *The Lancet* 2017;389(10073):1055-65. doi: https://doi.org/10.1016/S0140-6736(17)30553-6
31. Critical Appraisal Skills Programme (CASP). CASP (Qualitative) Checklist 2018 [Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-Download.pdf accessed 1 May 2018.

32. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Medical Research Methodology* 2008;8(1):45. doi: 10.1186/1471-2288-8-45

APPENDICES

Appendix 1. Inclusion/exclusion form for study selection

	Include	Yes	No	Unclear	Exclude	
Research type	▪ Qualitative study, standalone ▪ Qualitative study in the context of mixed method ▪ Review of qualitative studies ▪ Other, specify:	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Quantitative study ▪ Clearly commentary/letter with no data from primary studies ▪ Other, specify:	☐ ☐
If clearly excluded on study design – STOP HERE						
Sample	▪ Primary care Health professionals - General practitioner - Nurse practitioner - Other, specify: ▪ Patients treated in primary care	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	▪ Secondary or tertiary care health professionals ▪ Patients treated in Secondary or tertiary care	☐ ☐
Phenomenon of Interest	▪ Lipid lowering drugs initiation or prescription ▪ Antihypertensive drugs initiation or prescription ▪ Drug initiation or prescription for primary prevention of CVD	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Initiation or prescription of: - Aspirin - Fibrates - Niacin - Bile acid sequestrants - Omega-3 fatty acid compounds ▪ Adherence to medication ▪ Discontinuation of medication ▪ Other, specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐
Design	▪ Qualitative data collection, specify: ▪ Qualitative data analysis, specify:	☐ ☐	☐ ☐	☐ ☐	▪ Quantitative data collection or analysis with no qualitative component	☐

Evaluation	▪ Attitudes, perceptions, views, experiences, patient or health professional related Factors influencing cardiovascular drug initiation or prescription for primary prevention	☐	☐	☐	▪ Attitudes, perceptions, views, experiences, patient or health professional related factors influencing cardiovascular drug initiation or prescription for secondary prevention ☐ ▪ Factors influencing drug adherence or discontinuation ☐ ▪ Other, specify:
If “NO” in any of the categories, exclude					
Comments					

Appendix 2. Data collection form

Reviewer name (collecting data)		
Data collection date	Click or tap to enter a date.	
Reviewer name (reviewing collected data)		
Data review date	Click or tap to enter a date.	
Amendments		
Date of amendment	Click or tap to enter a date.	
Notes		
Study Bibliographic details		
First author		
Publication date	Click or tap to enter a date.	
Country		
Study characteristics		
Study type	☐Qualitative ☐Mixed method	
Study aim	What was the purpose or aim of the study	
Theoretical approach	What theoretical perspective is the study based on?	
Setting	What is the geographical location and setting of the study?	
Participants		
Type of participants	Who was included in the study	☐Patient ☐General practitioner ☐Nurse practitioner
Recruitment	How were participants recruited?	
Participants excluded	Were there any participants excluded?	☐Yes ☐No
	Reason of exclusion:	
Total number of participants		

Number of males		
Number of females		
Age of participants		
Methods		
Method of data collection	How was data collected?	☐Interview ☐Survey ☐Questionnaire ☐Focus group ☐Other
Additional details about data collection		
Data collection duration	What is the start and end date of the data collection?	
Method of data analysis	How was the data analysed?	
Additional details about data analysis		
Findings		
Main findings	What are the main findings of the study?	
Descriptive themes	What descriptive themes were reported?	
Author interpretation	What are the interpretations of results provided by the authors?	
Study strengths and weakness	What are the key strengths and weaknesses of the study?	

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

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

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

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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TITLE

Patients' and health professionals' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies

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KEYWORDS

systematic review; qualitative research; cardiovascular disease; attitudes; perceptions; drug initiation; statins; antihypertensive drugs; primary prevention

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ABSTRACT

Introduction: Lipid lowering drugs and antihypertensive agents can be prescribed for the primary prevention of cardiovascular disease. In some cases, patients eligible for primary prevention of cardiovascular disease according to the European guidelines are not always started on preventive drugs. Existing research explores the attitudes of health professionals and patients towards cardiovascular preventive drugs but does not always differentiate between the attitudes towards drug initiation for primary or secondary prevention. We aim to systematically review qualitative studies assessing health professionals' and patients' attitudes and perceptions towards drug initiation for primary prevention of cardiovascular disease.

Methods and analysis: MEDLINE, MEDLINE In Process, EMBASE, PsychINFO, CINAHL and Applied Social Sciences Index and Abstracts (ASSIA), Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey will be searched without restrictions on date or language of publication. Searches will be limited to studies of qualitative design, standalone or in the context of a mixed-method design, focusing on cardiovascular drug initiation for primary prevention. The primary outcome is the attitudes of health professionals and patients towards drug initiation for primary prevention of cardiovascular disease. Two reviewers will independently carry out the study selection, data extraction and quality assessment. The Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist will be used to assess the quality of included studies. The findings will be analysed using thematic synthesis.

Ethics and dissemination: This systematic review does not require ethical approval as primary data will not be collected. The results of the study will be published in a peer-reviewed journal and presented at relevant conferences.

Systematic review registration: PROSPERO CRD42018095346

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review will utilize a systematic approach to summarize qualitative evidence on preventive drug initiation in primary care settings.

- This review will focus on summarizing existing evidence regarding drug initiation for primary prevention of cardiovascular as recommended by the European guidelines.
- It will provide a better understanding of what influences health professionals' and patients' decisions regarding initiation of preventive treatment.
- The study will not review attitudes towards drug initiation in secondary or tertiary care settings.
- The study will not review studies addressing the initiation of aspirin for the primary prevention of cardiovascular disease.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of deaths worldwide [1]. It accounts for 26% of deaths in the United Kingdom and 31% of deaths globally [1 2]. One of the ways to prevent CVD is through prescribing drugs for primary prevention. National and international guidelines recommend primary preventive treatment for patients at an increased risk of developing a cardiovascular event [3-6]. Patients considered at an increased risk include patients who have a 10-year CVD risk of 10% or more or patients with clinically measured blood pressure of 140/90 mmHg or higher [4 6]. The recommendations are supported by evidence from clinical trials demonstrating the beneficial effects of lipid lowering drugs and antihypertensive agents in the primary prevention of CVD [7-10]. However, studies have reported low prescribing rates of preventive drugs [11-14]. Patients eligible for statins are undertreated [13 14]; one study has reported that 50% of patients with a CVD risk ≥20% were not prescribed statins for primary prevention [14]. In addition, the detection and treatment of hypertension remains low in parts of the world [15 16]. 49% of adults with hypertension aged 35-84 years were treated in Japan compared to 80% in the United States [15]. However, the initiation rate for antihypertensive drugs in younger eligible adults in the United States is suboptimal [17]. A study that explored antihypertensive drug initiation among young adults with regular access to primary care found that only 34% of patients aged 18-39 years were started on antihypertensive drugs compared to 44% of patients aged 40-59 years [17].

The suboptimal prescribing patterns may be a result of health professionals' poor adherence to guideline recommendations. A study conducted in German general practices estimated that around 50% of general practitioners (GPs) did not adhere to the guidelines [18]. GPs have expressed concerns regarding the evidence the guidelines

were based on and whether following the guidelines will allow them to meet their patients' needs [19 20]. Nevertheless, the variation in prescribing patterns indicates that there are patient- and GP-related barriers to initiating primary preventive treatment. Previous research identified GP-related barriers such as concerns about patient adherence to medication, over-medicalization of healthy individuals and side effects [21]. With respect to patient-related barriers, a study reported that patients preferred making lifestyle changes and had concerns about the side effects of taking medication [22]. In addition, patients' trust in their GP's medical judgment played a role in accepting preventive treatments [22].

We are interested in studies that explore the attitudes of health professionals and patients towards initiating treatments for the primary prevention of CVD. A scoping search was carried out to identify existing literature and to estimate the volume of studies available on our topic of interest. The majority of published studies address the issue of adherence to medication or prescribing drugs for secondary prevention [23 24]. However, the search retrieved a number of qualitative studies that investigate patient and health professional-related factors influencing drug prescribing for primary prevention. The search retrieved a systematic review published in 2012 that assessed qualitative literature about initiating and adhering to preventive drugs for CVD. The review discussed factors associated with initiating preventive medication and reported that initiation was influenced by the health professional-patient relationship and the organizational structure of the clinical environment [25]. The authors focused on starting and adhering to preventive medication with no differentiation between primary and secondary prevention. In addition, studies were excluded from the review based on quality assessment. Our review will consider all primary studies addressing our topic of interest regardless of quality to capture all available evidence regarding prescribing cardiovascular drugs for primary prevention. Furthermore, the search retrieved one recently published systematic review that explored patients' attitudes towards taking statins. However, the review did not explore the attitudes of health professionals towards statins and was restricted to studies in the English language [26]. The authors explored attitudes only towards statin uptake without differentiating between primary and secondary prevention. Both reviews did not explore grey literature. In this review we aim to explore grey literature databases to maximize the chances of capturing relevant studies.

Our review will add valuable information to the existing knowledge about CVD prevention. The existing reviews either assess the initiation of a specific drug, such as statins, or focus on the initiation of cardiovascular preventive drugs without differentiating between primary and secondary prevention. In this review we will include all preventive drugs to provide a comprehensive summary of evidence regarding health professionals' and patients' attitudes towards any cardiovascular drug recommended by the European guidelines for primary prevention. In addition, we choose to focus on drug initiation for primary prevention of CVD because the reasons behind taking cardiovascular preventive drugs such as statins might be different in patients who had a CVD event and patients who are yet to experience a CVD event. The initiation of preventive drugs in a relatively asymptomatic patient can be challenging for both the health professional and the patient, and attitudes relating to this preventive approach need to be identified for successful primary care preventive prescribing. The decision-making process involved in initiating preventive treatments is complex and influenced by multiple factors that relate to both the health professional and the patient. Thus, an up-to-date, methodologically robust systematic review aiming to identify the attitudes and perceptions of health professionals and patients towards the initiation of preventive drugs for the primary prevention of CVD is warranted.

Objectives

- Explore health professionals' attitudes and perceptions in relation to initiating preventive drugs for primary prevention of CVD in primary care settings.
- Explore patients' attitudes and perceptions towards initiating preventive drugs for primary prevention of CVD in primary care settings.

METHODS AND ANALYSIS

This protocol will use the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to ensure comprehensive reporting of study items [27]. The protocol is registered with PROSPERO (CRD42018095346). The systematic review will follow the reporting guidelines formulated in the Enhancing

transparency in reporting the synthesis of qualitative research (ENTREQ) statement [28].

Information sources and search strategy

The Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) tool is considered an alternative to PICOS when addressing a qualitative review question and will be used in the proposed systematic review to formulate the search strategy [29]. The search strategy will include a combination of free text words and index terms relating to (drug initiation OR prescription OR decision making) and (attitudes OR experiences OR perceptions OR views OR behaviour) and cardiovascular disease. Each element from the SPIDER tool will be included in the search strategy and potential alternative search terms will be included to maximize the chances of retrieving relevant studies. The formulated search strategy will be applied to MEDLINE database (including MEDLINE In Process) then adapted with necessary adjustments for use in other databases. The search strategy for MEDLINE is presented in (Appendix 1). We will search EMBASE, PsychINFO, CINAHL and Applied Social Sciences Index and Abstracts (ASSIA) for published studies. In addition, the following grey literature sources will be searched: Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey. The reference lists of included studies will be checked to identify additional eligible studies which were not retrieved by the formulated search strategy. There will be no restriction on date or language of publication. The search will be limited to studies of qualitative design.

Eligibility criteria

Sample

We will include studies of primary care health professionals (GPs and nurse practitioners), in any country, who prescribe cardiovascular preventive drugs. In addition, we will include studies that target patients who are offered a prescription for statins or antihypertensive drugs in a primary care setting. However, studies assessing drug initiation in older patients aged 85 or over will not be included as the considerations for primary prevention of CVD in an older age group are different with

additional factors that complicate drug prescription, such as multimorbidity and polypharmacy. Studies that focus on practitioners or patients involved in the process of decision making or initiation of cardiovascular drugs will be included. Any study that examines practitioners who prescribe preventive drugs and patients who receive such prescriptions for secondary prevention of CVD will be excluded. Studies conducted in secondary care settings will be excluded.

Phenomenon of interest

Studies will be considered for inclusion if they assess patient or practitioner factors associated with the initiation of cardiovascular preventive drugs in primary care settings. Initiation refers to the prescription of preventive drugs by the practitioner and the patient agreeing to take medication for preventive purposes. Therefore, studies that focus on decision making or discuss barriers and facilitators to prescription for primary prevention of CVD will be included. We will exclude studies that focus on adherence and continuation of cardiovascular preventive drugs.

Design / Research type

Our review aims to look at aspects such as attitudes and perceptions. These are best explored through a qualitative approach. Therefore, any qualitative studies, stand alone or in the context of a mixed-method design, focusing on cardiovascular drug prescription for primary prevention will be included. A summary of Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) is provided in table 1.

Table 1. Summary of Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER)

Sample	- Health professionals (General practitioners or nurse practitioners) who prescribe statins or antihypertensive drugs. - Patients eligible for cardiovascular preventive drugs or offered a prescription of statin or an antihypertensive drug for primary prevention of cardiovascular disease.
Phenomenon of Interest	The initiation or prescription of statins or antihypertensive drugs.
Design	Studies including qualitative data collection or analysis methods.

Evaluation	Attitudes, perceptions, views or experiences of health professionals or patients related to the initiation of cardiovascular preventive drugs.
Research type	Qualitative and mixed methods studies.

Evaluation

Studies that address the attitudes, perceptions, views or experiences of health professionals or patients involved in the process of cardiovascular preventive drug initiation will be considered for inclusion. To adhere to the European guidelines, we will include studies that target the prescription of statins or antihypertensive drugs [4 6]. We will exclude studies that target the prescription of aspirin as its use for primary prevention is not recommended by several guidelines [5 30]. In addition, studies that assess the attitudes and perceptions of practitioners or patients towards the prescribing of fibrates, niacin, bile acid sequestrants and Omega - 3 fatty acid compounds will be excluded as these drugs are not recommended for the primary prevention of CVD [4 5]. In some countries, a polypill that contains a lipid lowering agent and a blood pressure lowering agent is prescribed for CVD risk reduction [31]. Thus, we will consider studies that assess health professionals' and patients' attitudes towards polypills.

Selection process

The literature search results will be imported into Endnote X8 (Thomson Reuters, New York), to ensure efficient management of references and to facilitate the study selection process. The process of selecting studies will be carried out in two stages by two independent reviewers. The reviewers will follow explicit inclusion/exclusion criteria to minimize potential bias and to ensure minimal influence of the reviewers' preconceptions. The inclusion/exclusion form is presented in (Appendix 2). The first stage of selection will include screening the titles and abstracts of all identified records against the inclusion criteria. If a study addresses our topic but the abstract lacks sufficient information to assess eligibility for inclusion, the full text will be retrieved to make a definitive decision. In the second stage of selection the two reviewers will retrieve the full texts of included studies and assess them for eligibility. Any disagreements during the selection process will be resolved through discussion. If the

two reviewers fail to reach an agreement, a third independent reviewer will be involved for an unbiased decision. The reviewers will keep a record for each article that they have assessed and justify their decision for either inclusion or exclusion. The selection process will be piloted on a small number of studies by the main reviewer to ensure the reliability of the inclusion criteria. The selection process will be illustrated using a PRISMA flow diagram [27].

Data extraction process

An electronic standardised data extraction form will be developed to ensure adequate and consistent extraction of all required information. The form will be piloted using a small number of studies to ensure reliability and validity and adjusted if necessary. The electronic form will be used to record extracted data on study characteristics, participants' details, theoretical approach, data collection methods, data analysis and findings (Appendix 3). Once extraction is completed by the two reviewers, the forms will be reviewed, and any discrepancies will be resolved through discussion. If the two reviewers fail to reach agreement, a third reviewer will be involved.

Critical appraisal

Two independent reviewers will appraise the quality of the included studies using the Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist [32]. The assessment of quality will be based on the study aims, methodology, study design, sample recruitment, reflexivity, data collection, data analysis, findings, value of research and ethics. The reviewers will keep a record of the quality assessment for each study with an explanation of their decision. Any disagreements will be resolved by discussion or referral to a third independent reviewer. Studies will not be excluded from the review based on quality.

Data synthesis

The NVivo10 software will be used to analyse qualitative data. We will adopt a method of thematic synthesis defined by Thomas and Harden for synthesising qualitative data in systematic reviews [33]. Thematic synthesis includes three stages: First, line by line

examination of studies' findings and assigning codes to each line of text based on the meaning and content. Second, codes are then grouped into a hierarchical structure and organized as descriptive themes. Finally, analytical themes will be generated to provide interpretations that surpass the findings of the primary studies and ultimately answer our review question. The thematic synthesis will be carried out by two independent reviewers. The reviewers will discuss the codes and themes with an advisory team and then agree on the analytical stage of thematic synthesis.

Patient and public involvement

This protocol was completed without patient or public involvement. Patients were not invited to contribute to the development of this protocol. There are no plans to include patients in any stage of this systematic review. However, the findings of the review will be available to healthcare professionals, policy makers and the public.

DISCUSSION

The health professional's decision to prescribe a preventive drug and the patient's willingness to start treatment for preventive purposes is a multifactorial process. It is essential to understand this process of decision making from a qualitative perspective to enable a more effective approach to cardiovascular disease prevention. This review will summarize the qualitative evidence available on healthcare professionals' and patients' attitudes towards drug initiation. The findings will help us to understand the complex interaction that occurs during the consultation visit between the patient and their health professional and provide evidence to inform healthcare professionals and policy makers regarding barriers and facilitators to primary care cardiovascular preventive prescribing.

ETHICS AND DISSEMINATION

This review will utilize information available from primary studies. Data will not be collected from individuals therefore ethical approval is not required. We aim to disseminate the findings of our review through publication in a peer-reviewed journal and presentation at a relevant conference.

AUTHORS' CONTRIBUTIONS

OQ formulated the research question, performed the scoping search and wrote the first draft. OQ and DB refined research question and search strategy. TM, DB, NA reviewed and revised the draft. All authors read and approved the final manuscript.

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COMPETING INTERESTS

None declared.

REFERENCES

1. World Health Organization. Cardiovascular diseases: Fact sheets 2017 [Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ accessed 1 June 2018.
2. British Heart Foundation. CVD statistics - BHF UK factsheet: British Heart Foundation; 2018 [Available from: https://www.bhf.org.uk/research/heart-statistics accessed 1 June 2018.
3. Boon N, Boyle R, Bradbury K, et al. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100(Suppl 2):ii1-ii67. doi: 10.1136/heartjnl-2014-305693
4. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease London: NICE; 2014 [Available from: https://www.nice.org.uk/guidance/cg181 accessed 1 April 2017.
5. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Atherosclerosis* 2016;252:207-74. doi: 10.1016/j.atherosclerosis.2016.05.037
6. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management London: NICE; 2016 [Available from: https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2 accessed 1 April 2018.
7. Karmali KN, Lloyd-Jones DM, Berendsen MA, et al. Drugs for Primary Prevention of Atherosclerotic Cardiovascular Disease: An Overview of Systematic Reviews. *JAMA cardiology* 2016;1(3):341-9. doi: 10.1001/jamacardio.2016.0218 [published Online First: 2016/07/22]
8. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane database of systematic reviews* 2013(1):Cd004816. doi: 10.1002/14651858.CD004816.pub5 [published Online First: 2013/02/27]
9. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Archives of internal medicine* 2006;166(21):2307-13. doi: 10.1001/archinte.166.21.2307 [published Online First: 2006/11/30]
10. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2016;316(19):2008-24. doi: 10.1001/jama.2015.15629 [published Online First: 2016/11/14]
11. Turner GM, Calvert M, Feltham MG, et al. Under-prescribing of Prevention Drugs and Primary Prevention of Stroke and Transient Ischaemic Attack in UK General Practice: A Retrospective Analysis. *PLoS Medicine* 2016;13(11):e1002169. doi: 10.1371/journal.pmed.1002169
12. Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. *BMC health services research* 2014;14:414. doi: 10.1186/1472-6963-14-414 [published Online First: 2014/09/23]
13. Wu J, Zhu S, Yao GL, et al. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general

practice: a national retrospective cohort study. *PloS one* 2013;8(7):e67611. doi: 10.1371/journal.pone.0067611 [published Online First: 2013/08/08]
14. Homer K, Boomla K, Hull S, et al. Statin prescribing for primary prevention of cardiovascular disease: a cross-sectional, observational study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015;65(637):e538-44. doi: 10.3399/bjgp15X686113 [published Online First: 2015/07/28]
15. Ikeda N, Sapienza D, Guerrero R, et al. Control of hypertension with medication: a comparative analysis of national surveys in 20 countries. *Bulletin of the World Health Organization* 2014;92(1):10-19c. doi: 10.2471/blt.13.121954 [published Online First: 2014/01/07]
16. Baker R, Wilson A, Nockels K, et al. Levels of detection of hypertension in primary medical care and interventions to improve detection: a systematic review of the evidence since 2000. *BMJ Open* 2018;8(3):e019965. doi: 10.1136/bmjopen-2017-019965
17. Johnson HM, Thorpe CT, Bartels CM, et al. Antihypertensive Medication Initiation Among Young Adults with Regular Primary Care Use. *Journal of General Internal Medicine* 2014;29(5):723-31. doi: 10.1007/s11606-014-2790-4
18. Oriol-Zerbe C, Abholz HH. Primary prevention of cardiovascular diseases by lipid-lowering treatment in German general practice: results from GPs ignoring guidelines and risk calculators. *The European journal of general practice* 2007;13(1):27-34. doi: 10.1080/13814780601050541 [published Online First: 2007/03/17]
19. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2007;57(545):971-8. doi: 10.3399/096016407782604820 [published Online First: 2008/02/07]
20. Carlsen B, Norheim OF. "What lies beneath it all?" – an interview study of GPs' attitudes to the use of guidelines. *BMC health services research* 2008;8:218-18. doi: 10.1186/1472-6963-8-218
21. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice* 2003;53(494):684-89.
22. Gale NK, Greenfield S, Gill P, et al. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. *BMC Family Practice* 2011;12:59-59. doi: 10.1186/1471-2296-12-59
23. Fung V, Graetz I, Reed M, et al. Patient-reported adherence to statin therapy, barriers to adherence, and perceptions of cardiovascular risk. *PloS one* 2018;13(2):e0191817. doi: 10.1371/journal.pone.0191817
24. Jamison J, Graffy J, Mullis R, et al. Stroke survivors', caregivers' and GPs' attitudes towards a polypill for the secondary prevention of stroke: a qualitative interview study. *BMJ Open* 2016;6(5)
25. Gale N, Marshall T, Bramley G. Starting and staying on preventive medication for cardiovascular disease. *Current Opinion in Cardiology* 2012;27(5):533-41. doi: 10.1097/HCO.0b013e328356dae5

26. Ju A, Hanson CS, Banks E, et al. Patient beliefs and attitudes to taking statins: systematic review of qualitative studies. *British Journal of General Practice* 2018;68(671):e408-e19. doi: 10.3399/bjgp18X696365
27. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *The BMJ* 2009;339:b2700. doi: 10.1136/bmj.b2700
28. Tong A, Flemming K, McInnes E, et al. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Medical Research Methodology* 2012;12:181-81. doi: 10.1186/1471-2288-12-181
29. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qualitative health research* 2012;22(10):1435-43. doi: 10.1177/1049732312452938 [published Online First: 2012/07/26]
30. Aspirin: not licensed for primary prevention of thrombotic vascular disease 2009 [Available from: https://www.gov.uk/drug-safety-update/aspirin-not-licensed-for-primary-prevention-of-thrombotic-vascular-disease.
31. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *The Lancet* 2017;389(10073):1055-65. doi: https://doi.org/10.1016/S0140-6736(17)30553-6
32. Critical Appraisal Skills Programme (CASP). CASP (Qualitative) Checklist 2018 [Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-Download.pdf accessed 1 May 2018.
33. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Medical Research Methodology* 2008;8(1):45. doi: 10.1186/1471-2288-8-45

APPENDICES

Appendix 1. Medline search strategy

	Search term
1	Health personnel.mp.
2	Doctor*.mp.
3	Healthcare professional*.mp.
4	GENERAL PRACTITIONERS/ or FAMILY NURSE PRACTITIONERS/ or NURSE PRACTITIONERS/ or Practitioner*.mp.
5	Physician*.mp.
6	Prescriber*.mp.
7	Patient*.mp.
8	General Practice.mp. or General Practice/
9	Primary Health Care.mp. or Primary Health Care/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	(Prescrib* adj2 (lipid lowering drug* or Statin* or Ezetimibe or Blood pressure lowering drug* or Antihypertensive drug* or Angiotensin Converting Enzyme Inhibitor or ACE or Angiotensin Receptor Blocker or ARB or Calcium Channel Blocker* or Beta Blocker* or variation*)).mp.
12	((Drug or medication) adj2 (start* or tak* or receiv* or initiation or utilization or prescrib* or choice)).mp.
13	Decision making.mp. or Decision Making/
14	Preventive drug*.mp.
15	Preventive therap*.mp.
16	Antihypertensive Agents/tu [Therapeutic Use]
17	Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu [Therapeutic Use]
18	Statin*.mp.
19	Practice Patterns, Physicians'/
20	Physician-Patient Relations/
21	(Preventive adj2 (drug* or therap* or treatment* or medication)).mp.
22	Preventive Medicine/mt [Methods]
23	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	Cardiovascular Diseases/dt, pc [Drug Therapy, Prevention & Control]
25	(Cardiovascular adj3 primary prevention).mp.
26	(Cardiovascular preventive adj2 (drug* or therap* or treatment* or medication)).mp.
27	24 or 25 or 26
28	10 and 23 and 27
29	limit 28 to "qualitative (best balance of sensitivity and specificity)"
30	Qualitative.mp.
31	Mixed methods.mp.
32	Focus Groups*.mp.
33	Interview*.mp.
34	"Surveys and Questionnaires"/
35	Nursing Methodology Research/
36	30 or 31 or 32 or 33 or 34 or 35
37	"Attitude of Health Personnel"/
38	Attitude to Health/
39	Attitude*.mp.
40	Perception*.mp.
41	Prespective*.mp.
42	Behavio?r.mp.
43	View*.mp.

44	Experience*.mp.
45	Expectation*.mp.
46	Belie*.mp.
47	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	36 or 47
49	28 and 48
50	29 or 49

Appendix 2. Inclusion/exclusion form for study selection

	Include	Yes	No	Unclear	Exclude	
Research type	▪ Qualitative study, standalone ▪ Qualitative study in the context of mixed method ▪ Review of qualitative studies ▪ Other, specify:	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Quantitative study ▪ Clearly commentary/letter with no data from primary studies ▪ Other, specify:	☐ ☐
If clearly excluded on study design – STOP HERE						
Sample	▪ Primary care Health professionals - General practitioner - Nurse practitioner - Other, specify: ▪ Patients treated in primary care	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	▪ Secondary or tertiary care health professionals ▪ Patients treated in Secondary or tertiary care	☐ ☐
Phenomenon of Interest	▪ Lipid lowering drugs initiation or prescription ▪ Antihypertensive drugs initiation or prescription ▪ Drug initiation or prescription for primary prevention of CVD	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Initiation or prescription of: - Aspirin - Fibrates - Niacin - Bile acid sequestrants - Omega-3 fatty acid compounds ▪ Adherence to medication ▪ Discontinuation of medication ▪ Other, specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐
Design	▪ Qualitative data collection, specify: ▪ Qualitative data analysis, specify:	☐ ☐	☐ ☐	☐ ☐	▪ Quantitative data collection or analysis with no qualitative component	☐
Evaluation	▪ Attitudes, perceptions, views, experiences, patient or health	☐	☐	☐	▪ Attitudes, perceptions, views, experiences,	☐

	professional related Factors influencing cardiovascular drug initiation or prescription for primary prevention	patient or health professional related factors influencing cardiovascular drug initiation or prescription for secondary prevention ▪ Factors influencing drug adherence or discontinuation ☐ ▪ Other, specify:
If “NO” in any of the categories, exclude		
Comments		

Appendix 3. Data collection form

Reviewer name (collecting data)		
Data collection date	Click or tap to enter a date.	
Reviewer name (reviewing collected data)		
Data review date	Click or tap to enter a date.	
Amendments		
Date of amendment	Click or tap to enter a date.	
Notes		
Study Bibliographic details		
First author		
Publication date	Click or tap to enter a date.	
Country		
Study characteristics		
Study type	☐Qualitative ☐Mixed method	
Study aim	What was the purpose or aim of the study	
Theoretical approach	What theoretical perspective is the study based on?	
Setting	What is the geographical location and setting of the study?	
Participants		
Type of participants	Who was included in the study	☐Patient ☐General practitioner ☐Nurse practitioner
Recruitment	How were participants recruited?	
Participants excluded	Were there any participants excluded?	☐Yes ☐No
	Reason of exclusion:	
Total number of participants		

Number of males		
Number of females		
Age of participants		
Methods		
Method of data collection	How was data collected?	☐Interview ☐Survey ☐Questionnaire ☐Focus group ☐Other
Additional details about data collection		
Data collection duration	What is the start and end date of the data collection?	
Method of data analysis	How was the data analysed?	
Additional details about data analysis		
Findings		
Main findings	What are the main findings of the study?	
Descriptive themes	What descriptive themes were reported?	
Author interpretation	What are the interpretations of results provided by the authors?	
Study strengths and weakness	What are the key strengths and weaknesses of the study?	

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

Section and topic	Item No	Checklist item	Reported on page/line
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1/5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2/53
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1/9-12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11/302-305
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11/308
Sponsor	5b	Provide name for the review funder and/or sponsor	11/309
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5/100-142
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5/144-148, 7-8/209-211
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8/179-225
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6/158-177
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	Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8/228
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9/230-245
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9/247-255
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Appendix 3
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	9/257-265
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10/267-277
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

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

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Patients' and health professionals' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies

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Keywords:	systematic review, QUALITATIVE RESEARCH, cardiovascular disease, attitudes, drug initiation, primary prevention

TITLE

Patients' and health professionals' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies

AUTHORS

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KEYWORDS

systematic review; qualitative research; cardiovascular disease; attitudes; perceptions; drug initiation; statins; antihypertensive drugs; primary prevention

WORD COUNT

2617 words (excluding title page, abstract, references, figures and tables).

ABSTRACT

Introduction: Lipid lowering drugs and antihypertensive agents can be prescribed for the primary prevention of cardiovascular disease. In some cases, patients eligible for primary prevention of cardiovascular disease according to the European guidelines are not always started on preventive drugs. Existing research explores the attitudes of health professionals and patients towards cardiovascular preventive drugs but does not always differentiate between the attitudes towards drug initiation for primary or secondary prevention. We aim to systematically review qualitative studies assessing health professionals' and patients' attitudes and perceptions towards drug initiation for primary prevention of cardiovascular disease.

Methods and analysis: MEDLINE, MEDLINE In Process, EMBASE, PsychINFO, CINAHL and Applied Social Sciences Index and Abstracts (ASSIA), Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey will be searched without restrictions on date or language of publication. Searches will be limited to studies of qualitative design, standalone or in the context of a mixed-method design, focusing on cardiovascular drug initiation for primary prevention. The primary outcome is the attitudes of health professionals and patients towards drug initiation for primary prevention of cardiovascular disease. Two reviewers will independently carry out the study selection, data extraction and quality assessment. The Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist will be used to assess the quality of included studies. The findings will be analysed using Thomas and Hardens' thematic synthesis approach.

Ethics and dissemination: This systematic review does not require ethical approval as primary data will not be collected. The results of the study will be published in a peer-reviewed journal and presented at relevant conferences.

Systematic review registration: PROSPERO CRD42018095346

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review will utilize a systematic approach to summarize qualitative evidence on preventive drug initiation in primary care settings.

- This review will focus on summarizing existing evidence regarding drug initiation for primary prevention of cardiovascular disease as recommended by the European guidelines.
- It will provide a better understanding of what influences health professionals' and patients' decisions regarding initiation of preventive treatment.
- The study will not review attitudes towards drug initiation in secondary or tertiary care settings.
- The study will not review studies addressing the initiation of aspirin for the primary prevention of cardiovascular disease.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of deaths worldwide [1]. It accounts for 26% of deaths in the United Kingdom and 31% of deaths globally [1 2]. One of the ways to prevent CVD is through prescribing drugs for primary prevention. National and international guidelines recommend primary preventive treatment for patients at an increased risk of developing a cardiovascular event [3-6]. Patients considered at an increased risk include patients with clinically measured blood pressure of ≥140/90 mmHg or patients who have a 10-year CVD risk of 10% or more [4 6]. A patients' risk of developing CVD within the next 10 years can be predicted using a risk assessment tool such as QRISK2. The QRISK2 assessment tool calculates an individual CVD risk taking into account factors such as age, ethnicity, smoking status, systolic blood pressure, cholesterol/HDL ratio and Body Mass Index (BMI) [7]. The recommendations are supported by evidence from clinical trials demonstrating the beneficial effects of lipid lowering drugs and antihypertensive agents in the primary prevention of CVD [8-11]. However, studies have reported low prescribing rates of preventive drugs [12-15]. Patients eligible for statins are undertreated [14 15]; one study has reported that 50% of patients with a CVD risk ≥20% were not prescribed statins for primary prevention [15]. In addition, the detection and treatment of hypertension remains low in parts of the world [16 17]. 49% of adults with hypertension aged 35-84 years were treated in Japan compared to 80% in the United States [16]. However, the initiation rate for antihypertensive drugs in younger eligible adults in the United States is suboptimal [18]. A study that explored antihypertensive drug initiation among young adults with regular access to primary care found that only 34% of patients aged 18-39 years were started on antihypertensive drugs compared to 44% of patients aged 40-59 years [18]. This

variation in drug initiation observed across countries can be due to multiple factors, including health system, health professional and patient factors. The healthcare system can influence the patients' ability to access health services and the affordability of preventive drugs. The suboptimal prescribing patterns may be a result of health professionals' poor adherence to guideline recommendations. A study conducted in German general practices estimated that around 50% of general practitioners (GPs) did not adhere to the guidelines [19]. GPs have expressed concerns regarding the evidence the guidelines were based on and whether following the guidelines will allow them to meet their patients' needs [20 21]. Nevertheless, the variation in prescribing patterns indicates that there are patient- and GP-related barriers to initiating primary preventive treatment. Previous research identified GP-related barriers such as concerns about patient adherence to medication, over-medicalization of healthy individuals and side effects [22]. With respect to patient-related barriers, a study reported that patients preferred making lifestyle changes and had concerns about the side effects of taking medication [23]. In addition, patients' trust in their GP's medical judgment played a role in accepting preventive treatments [23].

We are interested in studies that explore the attitudes of health professionals and patients towards initiating treatments for the primary prevention of CVD. A scoping search was carried out to identify existing literature and to estimate the volume of studies available on our topic of interest. The majority of published studies address the issue of adherence to medication or prescribing drugs for secondary prevention [24 25]. However, the search retrieved a number of qualitative studies that investigate patient and health professional-related factors influencing drug prescribing for primary prevention. The search retrieved a systematic review published in 2012 that assessed qualitative literature about initiating and adhering to preventive drugs for CVD. The review discussed factors associated with initiating preventive medication and reported that initiation was influenced by the health professional-patient relationship and the organizational structure of the clinical environment [26]. The authors focused on starting and adhering to preventive medication with no differentiation between primary and secondary prevention. In addition, studies were excluded from the review based on quality assessment. Our review will consider all primary studies addressing our topic of interest regardless of quality to capture all available evidence regarding prescribing cardiovascular drugs for primary prevention. Furthermore, the search retrieved one

recently published systematic review that explored patients' attitudes towards taking statins. However, the review did not explore the attitudes of health professionals towards statins and was restricted to studies in the English language [27]. The authors explored attitudes only towards statin uptake without differentiating between primary and secondary prevention. Both reviews did not explore grey literature. In this review we aim to explore grey literature databases to maximize the chances of capturing relevant studies.

Our review will add valuable information to the existing knowledge about CVD prevention. The existing reviews either assess the initiation of a specific drug, such as statins, or focus on the initiation of cardiovascular preventive drugs without differentiating between primary and secondary prevention. In this review we will include all preventive drugs to provide a comprehensive summary of evidence regarding health professionals' and patients' attitudes towards any cardiovascular drug recommended by the European guidelines for primary prevention. In addition, we choose to focus on drug initiation for primary prevention of CVD because the reasons behind taking cardiovascular preventive drugs such as statins might be different in patients who had a CVD event and patients who are yet to experience a CVD event. The initiation of preventive drugs in a relatively asymptomatic patient can be challenging for both the health professional and the patient, and attitudes relating to this preventive approach need to be identified for successful primary care preventive prescribing. The decision-making process involved in initiating preventive treatments is complex and influenced by multiple factors that relate to both the health professional and the patient. Thus, an up-to-date, methodologically robust systematic review aiming to identify the attitudes and perceptions of health professionals and patients towards the initiation of preventive drugs for the primary prevention of CVD is warranted.

Objectives

- Explore health professionals' attitudes and perceptions in relation to initiating preventive drugs for primary prevention of CVD in primary care settings.
- Explore patients' attitudes and perceptions towards initiating preventive drugs for primary prevention of CVD in primary care settings.

METHODS AND ANALYSIS

This protocol will use the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to ensure comprehensive reporting of study items [28]. The protocol is registered with PROSPERO (CRD42018095346). The systematic review will follow the reporting guidelines formulated in the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement [29].

Information sources and search strategy

The Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) tool is considered an alternative to PICOS when addressing a qualitative review question and will be used in the proposed systematic review to formulate the search strategy [30]. The search strategy will include a combination of free text words and index terms relating to (drug initiation OR prescription OR decision making) and (attitudes OR experiences OR perceptions OR views OR behaviour) and cardiovascular disease. Each element from the SPIDER tool will be included in the search strategy and potential alternative search terms will be included to maximize the chances of retrieving relevant studies. The formulated search strategy will be applied to MEDLINE database (including MEDLINE In Process) then adapted with necessary adjustments for use in other databases. The search strategy for MEDLINE is presented in (Appendix 1). We will search EMBASE, PsychINFO, CINAHL and Applied Social Sciences Index and Abstracts (ASSIA) for published studies. In addition, the following grey literature sources will be searched: Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium (HMIC) and Open Grey. The reference lists of included studies will be checked to identify additional eligible studies which were not retrieved by the formulated search strategy. There will be no restriction on date or language of publication. The search will be limited to studies of qualitative design and mixed methods design with a qualitative component.

Eligibility criteria

Sample

We will include studies of primary care health professionals (GPs and nurse practitioners), in any country, who prescribe cardiovascular preventive drugs. In addition, we will include studies that target patients who are offered a prescription for statins or antihypertensive drugs in a primary care setting. However, studies that specifically focus on drug initiation in older patients will not be included as the considerations for primary prevention of CVD in an older age group are different with additional factors that complicate drug prescription, such as multimorbidity and polypharmacy. Studies that focus on practitioners or patients involved in the process of decision making or initiation of cardiovascular drugs will be included. Any study that examines practitioners who prescribe preventive drugs and patients who receive such prescriptions for secondary prevention of CVD will be excluded. Studies conducted in secondary care settings will be excluded.

Phenomenon of interest

Studies will be considered for inclusion if they assess patient or practitioner factors associated with the initiation of cardiovascular preventive drugs in primary care settings. Initiation refers to the prescription of preventive drugs by the practitioner and the patient agreeing to take medication for preventive purposes. Therefore, studies that focus on decision making or discuss barriers and facilitators to prescription for primary prevention of CVD will be included. We will exclude studies that focus on adherence and continuation of cardiovascular preventive drugs.

Design / Research type

Our review aims to look at aspects such as attitudes and perceptions. These are best explored through a qualitative approach. Therefore, any qualitative studies, stand alone or in the context of a mixed-method design, focusing on cardiovascular drug prescription for primary prevention will be included. A summary of Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) is provided in table 1.

Table 1. Summary of Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER)

Sample	- Health professionals (General practitioners or nurse practitioners) who prescribe statins or antihypertensive drugs. - Patients eligible for cardiovascular preventive drugs or offered a prescription of statin or an antihypertensive drug for primary prevention of cardiovascular disease.
Phenomenon of Interest	The initiation or prescription of statins or antihypertensive drugs.
Design	Studies including qualitative data collection or analysis methods.
Evaluation	Attitudes, perceptions, views or experiences of health professionals or patients related to the initiation of cardiovascular preventive drugs.
Research type	Qualitative and mixed methods studies.

Evaluation

Studies that address the attitudes, perceptions, views or experiences of health professionals or patients involved in the process of cardiovascular preventive drug initiation will be considered for inclusion. To adhere to the European guidelines, we will include studies that target the prescription of statins or antihypertensive drugs [4 6]. We will exclude studies that target the prescription of aspirin as its use for primary prevention is not recommended by several guidelines [5 31]. In addition, studies that assess the attitudes and perceptions of practitioners or patients towards the prescribing of fibrates, niacin, bile acid sequestrants and Omega - 3 fatty acid compounds will be excluded as these drugs are not recommended for the primary prevention of CVD [4 5]. In some countries, a polypill that contains a lipid lowering agent and a blood pressure lowering agent is prescribed for CVD risk reduction [32]. Thus, we will consider studies that assess health professionals' and patients' attitudes towards polypills.

Selection process

The literature search results will be imported into Endnote X8 (Thomson Reuters, New York), to ensure efficient management of references and to facilitate the study

selection process. The process of selecting studies will be carried out in two stages by two independent reviewers. The reviewers will follow explicit inclusion/exclusion criteria to minimize potential bias and to ensure minimal influence of the reviewers' preconceptions. The inclusion/exclusion form is presented in (Appendix 2). The first stage of selection will include screening the titles and abstracts of all identified records against the inclusion criteria. If a study addresses our topic but the abstract lacks sufficient information to assess eligibility for inclusion, the full text will be retrieved to make a definitive decision. In the second stage of selection the two reviewers will retrieve the full texts of included studies and assess them for eligibility. Any disagreements during the selection process will be resolved through discussion. If the two reviewers fail to reach an agreement, a third independent reviewer will be involved for an unbiased decision. The reviewers will keep a record for each article that they have assessed and justify their decision for either inclusion or exclusion. The selection process will be piloted on a small number of studies by the main reviewer to ensure the reliability of the inclusion criteria. The selection process will be illustrated using a PRISMA flow diagram [28].

Data extraction process

An electronic standardised data extraction form will be developed to ensure adequate and consistent extraction of all required information. The form will be piloted using a small number of studies to ensure reliability and validity and adjusted if necessary. The electronic form will be used to record extracted data on study characteristics, participants' details, theoretical approach, data collection methods, data analysis and findings (Appendix 3). Once extraction is completed by the two reviewers, the forms will be reviewed, and any discrepancies will be resolved through discussion. If the two reviewers fail to reach agreement, a third reviewer will be involved.

Critical appraisal

Two independent reviewers will appraise the quality of the included studies using the Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist [33]. The assessment of quality will be based on the study aims, methodology, study design, sample recruitment, reflexivity, data collection, data analysis, findings, value of

research and ethics. The reviewers will keep a record of the quality assessment for each study with an explanation of their decision. Any disagreements will be resolved by discussion or referral to a third independent reviewer. Studies will not be excluded from the review based on quality.

Data synthesis

The NVivo10 software will be used to analyse qualitative data. We will adopt a method of thematic synthesis defined by Thomas and Harden for synthesising qualitative data in systematic reviews [34]. Thematic synthesis includes three stages: First, line by line examination of studies' findings and assigning codes to each line of text based on the meaning and content. Second, codes are then grouped into a hierarchical structure and organized as descriptive themes. Finally, analytical themes will be generated to provide interpretations that surpass the findings of the primary studies and ultimately answer our review question. The thematic synthesis will be carried out by two independent reviewers. The reviewers will discuss the codes and themes with an advisory team and then agree on the analytical stage of thematic synthesis.

Patient and public involvement

This protocol was completed without patient or public involvement. There were no funds or time allocated for patient and public involvement. Therefore, patients were not invited to contribute to the development of this protocol. There are no plans to include patients in any stage of this systematic review. However, the findings of the review will be available to healthcare professionals, policy makers and the public.

DISCUSSION

The health professional's decision to prescribe a preventive drug and the patient's willingness to start treatment for preventive purposes is a multifactorial process. It is essential to understand this process of decision making from a qualitative perspective to enable a more effective approach to cardiovascular disease prevention. This review will summarize the qualitative evidence available on healthcare professionals' and patients' attitudes towards drug initiation. The findings will help us to understand the

complex interaction that occurs during the consultation visit between the patient and their health professional and provide evidence to inform healthcare professionals and policy makers regarding barriers and facilitators to primary care cardiovascular preventive prescribing.

ETHICS AND DISSEMINATION

This review will utilize information available from primary studies. Data will not be collected from individuals therefore ethical approval is not required. We aim to disseminate the findings of our review through publication in a peer-reviewed journal and presentation at a relevant conference.

AUTHORS' CONTRIBUTIONS

OQ formulated the research question, performed the scoping search and wrote the first draft. OQ and DB refined research question and search strategy. TM, DB, NA reviewed and revised the draft. All authors read and approved the final manuscript.

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COMPETING INTERESTS

None declared.

REFERENCES

1. World Health Organization. Cardiovascular diseases: Fact sheets 2017 [Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ accessed 1 June 2018.
2. British Heart Foundation. CVD statistics - BHF UK factsheet: British Heart Foundation; 2018 [Available from: https://www.bhf.org.uk/research/heart-statistics accessed 1 June 2018.
3. Boon N, Boyle R, Bradbury K, et al. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100(Suppl 2):ii1-ii67. doi: 10.1136/heartjnl-2014-305693
4. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease London: NICE; 2014 [Available from: https://www.nice.org.uk/guidance/cg181 accessed 1 April 2017.
5. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Atherosclerosis* 2016;252:207-74. doi: 10.1016/j.atherosclerosis.2016.05.037
6. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management London: NICE; 2016 [Available from: https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2 accessed 1 April 2018.
7. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82. doi: 10.1136/bmj.39609.449676.25
8. Karmali KN, Lloyd-Jones DM, Berendsen MA, et al. Drugs for Primary Prevention of Atherosclerotic Cardiovascular Disease: An Overview of Systematic Reviews. *JAMA cardiology* 2016;1(3):341-9. doi: 10.1001/jamacardio.2016.0218 [published Online First: 2016/07/22]
9. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *The Cochrane database of systematic reviews* 2013(1):Cd004816. doi: 10.1002/14651858.CD004816.pub5 [published Online First: 2013/02/27]
10. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Archives of internal medicine* 2006;166(21):2307-13. doi: 10.1001/archinte.166.21.2307 [published Online First: 2006/11/30]
11. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2016;316(19):2008-24. doi: 10.1001/jama.2015.15629 [published Online First: 2016/11/14]
12. Turner GM, Calvert M, Feltham MG, et al. Under-prescribing of Prevention Drugs and Primary Prevention of Stroke and Transient Ischaemic Attack in UK General Practice: A Retrospective Analysis. *PLoS Medicine* 2016;13(11):e1002169. doi: 10.1371/journal.pmed.1002169
13. Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. *BMC health services research* 2014;14:414. doi: 10.1186/1472-6963-14-414 [published Online First: 2014/09/23]

14. Wu J, Zhu S, Yao GL, et al. Patient Factors Influencing the Prescribing of Lipid Lowering Drugs for Primary Prevention of Cardiovascular Disease in UK General Practice: A National Retrospective Cohort Study. *PLoS ONE* 2013;8(7):e67611. doi: 10.1371/journal.pone.0067611
15. Homer K, Boomla K, Hull S, et al. Statin prescribing for primary prevention of cardiovascular disease: a cross-sectional, observational study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015;65(637):e538-44. doi: 10.3399/bjgp15X686113 [published Online First: 2015/07/28]
16. Ikeda N, Sapienza D, Guerrero R, et al. Control of hypertension with medication: a comparative analysis of national surveys in 20 countries. *Bulletin of the World Health Organization* 2014;92(1):10-19c. doi: 10.2471/blt.13.121954 [published Online First: 2014/01/07]
17. Baker R, Wilson A, Nockels K, et al. Levels of detection of hypertension in primary medical care and interventions to improve detection: a systematic review of the evidence since 2000. *BMJ Open* 2018;8(3):e019965. doi: 10.1136/bmjopen-2017-019965
18. Johnson HM, Thorpe CT, Bartels CM, et al. Antihypertensive Medication Initiation Among Young Adults with Regular Primary Care Use. *Journal of General Internal Medicine* 2014;29(5):723-31. doi: 10.1007/s11606-014-2790-4
19. Oriol-Zerbe C, Abholz HH. Primary prevention of cardiovascular diseases by lipid-lowering treatment in German general practice: results from GPs ignoring guidelines and risk calculators. *The European journal of general practice* 2007;13(1):27-34. doi: 10.1080/13814780601050541 [published Online First: 2007/03/17]
20. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2007;57(545):971-8. doi: 10.3399/096016407782604820 [published Online First: 2008/02/07]
21. Carlsen B, Norheim OF. "What lies beneath it all?" – an interview study of GPs' attitudes to the use of guidelines. *BMC health services research* 2008;8:218-18. doi: 10.1186/1472-6963-8-218
22. Kedward J, Dakin L. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *The British Journal of General Practice* 2003;53(494):684-89.
23. Gale NK, Greenfield S, Gill P, et al. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. *BMC Family Practice* 2011;12:59-59. doi: 10.1186/1471-2296-12-59
24. Fung V, Graetz I, Reed M, et al. Patient-reported adherence to statin therapy, barriers to adherence, and perceptions of cardiovascular risk. *PloS one* 2018;13(2):e0191817. doi: 10.1371/journal.pone.0191817
25. Jamison J, Graffy J, Mullis R, et al. Stroke survivors', caregivers' and GPs' attitudes towards a polypill for the secondary prevention of stroke: a qualitative interview study. *BMJ Open* 2016;6(5)
26. Gale N, Marshall T, Bramley G. Starting and staying on preventive medication for cardiovascular disease. *Current Opinion in Cardiology* 2012;27(5):533-41. doi: 10.1097/HCO.0b013e328356dae5

27. Ju A, Hanson CS, Banks E, et al. Patient beliefs and attitudes to taking statins: systematic review of qualitative studies. *British Journal of General Practice* 2018;68(671):e408-e19. doi: 10.3399/bjgp18X696365
28. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *The BMJ* 2009;339:b2700. doi: 10.1136/bmj.b2700
29. Tong A, Flemming K, McInnes E, et al. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Medical Research Methodology* 2012;12:181-81. doi: 10.1186/1471-2288-12-181
30. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qualitative health research* 2012;22(10):1435-43. doi: 10.1177/1049732312452938 [published Online First: 2012/07/26]
31. Aspirin: not licensed for primary prevention of thrombotic vascular disease 2009 [Available from: https://www.gov.uk/drug-safety-update/aspirin-not-licensed-for-primary-prevention-of-thrombotic-vascular-disease.
32. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *The Lancet* 2017;389(10073):1055-65. doi: https://doi.org/10.1016/S0140-6736(17)30553-6
33. Critical Appraisal Skills Programme (CASP). CASP (Qualitative) Checklist 2018 [Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-Download.pdf accessed 1 May 2018.
34. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Medical Research Methodology* 2008;8(1):45. doi: 10.1186/1471-2288-8-45

APPENDICES

Appendix 1. Medline search strategy

	Search term
1	Health personnel.mp.
2	Doctor*.mp.
3	Healthcare professional*.mp.
4	GENERAL PRACTITIONERS/ or FAMILY NURSE PRACTITIONERS/ or NURSE PRACTITIONERS/ or Practitioner*.mp.
5	Physician*.mp.
6	Prescriber*.mp.
7	Patient*.mp.
8	General Practice.mp. or General Practice/
9	Primary Health Care.mp. or Primary Health Care/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	(Prescrib* adj2 (lipid lowering drug* or Statin* or Ezetimibe or Blood pressure lowering drug* or Antihypertensive drug* or Angiotensin Converting Enzyme Inhibitor or ACE or Angiotensin Receptor Blocker or ARB or Calcium Channel Blocker* or Beta Blocker* or variation*)).mp.
12	((Drug or medication) adj2 (start* or tak* or receiv* or initiation or utilization or prescrib* or choice)).mp.
13	Decision making.mp. or Decision Making/
14	Preventive drug*.mp.
15	Preventive therap*.mp.
16	Antihypertensive Agents/tu [Therapeutic Use]
17	Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu [Therapeutic Use]
18	Statin*.mp.
19	Practice Patterns, Physicians'/
20	Physician-Patient Relations/
21	(Preventive adj2 (drug* or therap* or treatment* or medication)).mp.
22	Preventive Medicine/mt [Methods]
23	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	Cardiovascular Diseases/dt, pc [Drug Therapy, Prevention & Control]
25	(Cardiovascular adj3 primary prevention).mp.
26	(Cardiovascular preventive adj2 (drug* or therap* or treatment* or medication)).mp.
27	24 or 25 or 26
28	10 and 23 and 27
29	limit 28 to "qualitative (best balance of sensitivity and specificity)"
30	Qualitative.mp.
31	Mixed methods.mp.
32	Focus Groups*.mp.
33	Interview*.mp.
34	"Surveys and Questionnaires"/
35	Nursing Methodology Research/
36	30 or 31 or 32 or 33 or 34 or 35
37	"Attitude of Health Personnel"/
38	Attitude to Health/
39	Attitude*.mp.
40	Perception*.mp.
41	Prespective*.mp.
42	Behavio?r.mp.
43	View*.mp.

44	Experience*.mp.
45	Expectation*.mp.
46	Belie*.mp.
47	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	36 or 47
49	28 and 48
50	29 or 49

Appendix 2. Inclusion/exclusion form for study selection

	Include	Yes	No	Unclear	Exclude	
Research type	▪ Qualitative study, standalone ▪ Qualitative study in the context of mixed method ▪ Review of qualitative studies ▪ Other, specify:	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Quantitative study ▪ Clearly commentary/letter with no data from primary studies ▪ Other, specify:	☐ ☐
If clearly excluded on study design – STOP HERE						
Sample	▪ Primary care Health professionals - General practitioner - Nurse practitioner - Other, specify: ▪ Patients treated in primary care	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	▪ Secondary or tertiary care health professionals ▪ Patients treated in Secondary or tertiary care	☐ ☐
Phenomenon of Interest	▪ Lipid lowering drugs initiation or prescription ▪ Antihypertensive drugs initiation or prescription ▪ Drug initiation or prescription for primary prevention of CVD	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	▪ Initiation or prescription of: - Aspirin - Fibrates - Niacin - Bile acid sequestrants - Omega-3 fatty acid compounds ▪ Adherence to medication ▪ Discontinuation of medication ▪ Other, specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐
Design	▪ Qualitative data collection, specify: ▪ Qualitative data analysis, specify:	☐ ☐	☐ ☐	☐ ☐	▪ Quantitative data collection or analysis with no qualitative component	☐
Evaluation	▪ Attitudes, perceptions, views, experiences, patient or health	☐	☐	☐	▪ Attitudes, perceptions, views, experiences,	☐

	professional related Factors influencing cardiovascular drug initiation or prescription for primary prevention	patient or health professional related factors influencing cardiovascular drug initiation or prescription for secondary prevention ▪ Factors influencing drug adherence or discontinuation ☐ ▪ Other, specify:
If “NO” in any of the categories, exclude		
Comments		

Appendix 3. Data collection form

Reviewer name (collecting data)		
Data collection date	Click or tap to enter a date.	
Reviewer name (reviewing collected data)		
Data review date	Click or tap to enter a date.	
Amendments		
Date of amendment	Click or tap to enter a date.	
Notes		
Study Bibliographic details		
First author		
Publication date	Click or tap to enter a date.	
Country		
Study characteristics		
Study type	☐Qualitative ☐Mixed method	
Study aim	What was the purpose or aim of the study	
Theoretical approach	What theoretical perspective is the study based on?	
Setting	What is the geographical location and setting of the study?	
Participants		
Type of participants	Who was included in the study	☐Patient ☐General practitioner ☐Nurse practitioner
Recruitment	How were participants recruited?	
Participants excluded	Were there any participants excluded?	☐Yes ☐No
	Reason of exclusion:	
Total number of participants		

Number of males		
Number of females		
Age of participants		
Methods		
Method of data collection	How was data collected?	☐Interview ☐Survey ☐Questionnaire ☐Focus group ☐Other
Additional details about data collection		
Data collection duration	What is the start and end date of the data collection?	
Method of data analysis	How was the data analysed?	
Additional details about data analysis		
Findings		
Main findings	What are the main findings of the study?	
Descriptive themes	What descriptive themes were reported?	
Author interpretation	What are the interpretations of results provided by the authors?	
Study strengths and weakness	What are the key strengths and weaknesses of the study?	

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

Section and topic	Item No	Checklist item	Reported on page/line
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1/5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2/54
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1/9-12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11/312-315
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11/318
Sponsor	5b	Provide name for the review funder and/or sponsor	11/319
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5/108-150
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5/152-156, 8/217-219
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-8/187-233
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6/166-185
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	Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8/236-238
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9/238-253
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9/255-263
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Appendix 3
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	9/265-273
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10/275-285
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

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

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