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Title page

Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Cardiovascular disease is estimated to affect 423 million people globally. It caused 18 million deaths in 2017 and is projected to cost USD$1 trillion by 2030 worldwide. Coronary artery disease (CAD) is the most common type of cardiovascular disease; CAD treatments can affect patients' quality of life. Valuations of quality of life or health utilities are important for economic evaluations to ascertain relative health benefit when comparing treatments, and can be expected to change for individuals over time. The purpose of this systematic review is to estimate the quality of life of CAD patients reported through the EuroQol EQ-5D questionnaire, from short to longer-term time points following different treatments.

Methods and analysis

PubMed, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website will be systematically searched from 2003 to 2020. Published, peer-reviewed, English language studies assessing quality of life of CAD patients using the EQ-5D will be included. One researcher will conduct the search; two researchers will independently screen titles and abstracts for potential inclusion. Full texts of potentially eligible studies will be retrieved for a second round of independent screening against inclusion and exclusion criteria by two researchers. The final list of included studies will be assessed for risk of bias using the Rob 2 and ROBINS-I tools for randomized and non-randomized studies, respectively. Data extraction will be done by one researcher, with data extraction for a random 10% of included studies checked by a second researcher. Mean utility weights for individual studies will be combined using random effects model meta-analyses. A model will be run separately for each time point and treatment. Treatment time points of interest include baseline, 30 days, 6 months, 12-24 months, and more than 24 months. Subgroup analysis of patients with diabetes who received interventional treatments — coronary artery bypass graft or percutaneous coronary intervention with or without stents, will be conducted for the same selected time points.

Ethics and dissemination: Ethics approval is not required for systematic reviews. Results of the review will be disseminated via publication in a peer-reviewed journal.

PROSPERO registration number: Pending

Key words:

Coronary artery disease; quality of life; EQ-5D; coronary artery bypass graft; percutaneous coronary intervention.

ARTICLE SUMMARY

Strengths and limitations of this study

- The search strategy is designed to be comprehensive and aligned with the Peer Review of Electronic Search Strategies (PRESS) guidelines.(1)
- We will use PubMed as one of the databases instead of Medline to capture articles not yet indexed with MeSH terms and those released ahead of print.
- A final search will be run just before data synthesis begins to find any new articles that should be included in the analysis, since the search.
- The systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(2)
- Inclusion of studies that are available as full text and in English only may lead to language bias.

INTRODUCTION

Cardiovascular disease affects 423 million people globally(3) and causes 31% of deaths annually with 18 million deaths in 2017.(4) Cardiovascular disease is projected to cost USD$1 trillion by 2030 in direct healthcare costs, lost productivity due to disability or premature death, and time lost from work.(5) Coronary artery disease (CAD) is the most common type of cardiovascular disease.(6) Patients with CAD are treated with long-term medications, lifestyle modifications, and/or interventional procedures.(7) Commonly used interventional procedures include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) with or without stents.(7)

Individuals living with CAD experience changes in their quality of life.(8-11) CAD treatments can affect quality of life in either a positive or negative direction; and this can be expected to change over a period of time, particularly in the immediate vs. longer-term period post-CABG or PCI.(8, 9) Quality of life estimates as measured by health utilities are important for economic evaluations to determine relative health benefit when comparing treatments.(12) Health utilities are the numerical value reflecting the strength of an individual's preference for specific health-related outcomes, where 0 represents death and 1 represents full health.(12) Together with length of life, health utilities are used to calculate quality-adjusted life years (QALYs).(12) QALYs are used in cost-effectiveness studies to enable direct comparisons between treatment options.(12)

For chronic illnesses such as coronary artery disease, health utilities over time are particularly important so as not to bias estimates of cost-effectiveness toward treatments that show early but unsustained health benefits, and against those which may only show health benefits in the longer-term.(8) However, health utilities over various time points can be logistically challenging and expensive to collect; and estimates need to be as robust as possible given their use in informing medical decision-making and health-related policies. Hence, to reduce research waste and to increase the robustness of utility estimates, systematic reviews and meta-analyses of health utilities from single studies are conducted.

Previous reviews and meta-analyses of health utilities in cardiovascular diseases focussed on either summarising preference weights of various health-related quality of life instruments(13) or in

synthesising the evidence on the validity and reliability of the EQ-5D.(14) Although the 2010 review by Dyer et al. summarised utility scores of the EQ-5D,(14) a number of important studies such as the ORBITA trial have since been published.(15) We will focus on studies that used the EQ-5D to measure health-related quality of life, as it is the most widely used generic preference-based instrument.(16) The EQ-5D is also the preferred instrument for Health Technology Assessments by the UK National Institute for Health and Care Excellence (NICE), and the Zorginstituut Nederland (ZIN).(16, 17)

The aim of this study is to estimate the quality of life of people with CAD quantified by the EQ-5D at selected time points (short-, mid- and longer-term) following the initiation of different treatments.

Box 1. Definitions

- Coronary artery disease: Any one of the following conditions — coronary atherosclerosis, angina, acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI).
- Optimal medical therapy: A combination of medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological).
- Interventional procedures: Coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) with — bare metal stent (PCI-BMS), drug-eluting stent (PCI-DES), absorbable stent (PCI-AS) or without stents (balloon angioplasty), carried out in addition to optimal medical therapy.
- Tariff: Preference weight which reflects the preference on different health states of a particular population.

METHODS AND ANALYSIS

Study design

The study protocol has been developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(2)

Search strategy

Databases

The following databases and sources will be searched: PubMed, Embase (Ovid), Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website.

A previous study demonstrated that to optimize the search when conducting systematic reviews, the following four electronic databases should be searched as a minimum: Medline, Embase, Web of Science, and Google Scholar.(18) We selected PubMed as it has a larger repository than Medline, including additional life sciences journals, citations that are “ahead of print” and those not yet indexed with MeSH terms.(19) We did not select Google Scholar as the search may not be replicable.

Timeframe

The search will encompass the following period: 1 January 2003 to the date of the first search in 2020. Where the search functions of particular databases do not allow day/month/year to be specified, we will use the month and year e.g. January 2003 to March 2020.

The lower date limit of January 2003 was selected as the first commercially available drug-eluting stent was approved by the US Food and Drug Administration in that year.(20) The upper date limit will be the date of the first search conducted (within the second search in the three-step strategy below); and will subsequently be used as the upper date limit when searching the remaining databases. This strategy ensures that the date range for searches is consistent across all databases.

Search strategy

The search aims to find both published and "ahead of print" publications. A three-step strategy will be used.

1. First search (EL): Initial search limited to PubMed only, followed by analysis of text words in the (a) titles and abstracts of retrieved papers (keywords); and (b) index terms used to describe the articles (metadata, tags). Keywords for the initial search: coronary artery disease; EQ-5D; EQ-5D-3L; EQ-5D-5L; EuroQol~~L~~; treatment. Output: The search string for the systematic review will be constructed.
2. Second search (EL): PubMed, Embase (Ovid), Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website will then be searched using the search string constructed from the previous step. The yield from this step will be subjected to title and abstract screening for potential inclusion (first screening), followed by retrieval of full text articles, and screening of full text articles for inclusion (second screening).
3. Third search (EL): The reference list of included articles will be manually examined to identify additional studies for inclusion in the systematic review.

Finally, as per good practice, searches will be re-run just before data synthesis to identify any new studies that should be retrieved for inclusion.

The following is a preliminary example of a search strategy for PubMed which will be refined/confirmed after the first search outlined above:

((((((((((coronary artery disease) OR (coronary heart disease)) OR (coronary atherosclerosis)) OR (myocardial infarction)) OR (acute coronary syndrome)) OR (angina)))) AND ((EQ-5D) OR (EuroQol)))) NOT ((editorial)) OR (conference proceeding))

The final search strategy will be provided to PROSPERO once the review has been completed.

Types of studies to be included

All types of studies will be included so long as inclusion criteria are met. Systematic reviews identified from the search will be examined for relevant studies for inclusion.

Inclusion criteria

- Studies which report on quality of life post-treatment for coronary artery disease — coronary atherosclerosis, angina, acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI)
- Treatments may be pharmacological, non-pharmacological (e.g. lifestyle modifications), or interventional procedures (e.g. coronary artery bypass graft, percutaneous coronary intervention with or without stents)
- Preference based utility values for quality of life using EQ-5D
- Studies reported in English

Exclusion criteria

- Editorials, letters, and conference proceedings
- Study protocols or studies-in-progress e.g. clinical trial registrations
- Studies which reported only EQ-5D Visual Analogue Scale outcomes
- Studies which reported EQ-5D values derived from mapping other measures of health outcomes
- Studies which reported quality of life from other studies, without contributing new data
- Studies which reported on subgroups of a previously reported dataset
- Highly specific patient groups e.g. studies examining coronary artery disease in people with depression
- For post-treatment estimates, treatment was not specified e.g. did not report the type of stent used
- Studies on enhanced external counter pulsation (EECP) therapy
- Full text article not available

Condition or domain being studied

Quality of life (health utilities) at various treatment time points for coronary artery disease.

Participants/population

Inclusion: Adults (18 years old and above) diagnosed with coronary artery disease using criteria such as the International Classification of Diseases and Related Health Problems (ICD-10).

Exclusion: People under 18 years old. Highly specific patient groups e.g. studies examining coronary artery disease in people with depression

Interventions

Pharmacological, non-pharmacological, and interventional procedures.

Pharmacological interventions are medications used to manage or treat coronary artery disease and/or prevent secondary cardiovascular events, and may include cholesterol-modifying medications, antiplatelets, beta blockers, calcium channel blockers, ranolazine, nitrates, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB).

Non-pharmacological interventions include lifestyle modifications such as smoking cessation, choosing healthy foods, engaging in regular physical activity/exercise, removing excess weight, and reducing stress.

Interventional procedures: Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) with or without stents (e.g. balloon angioplasty). Stents used in PCI may be bare metal stents, drug-eluting stents, absorbable stents, or absorbable drug-eluting stents.

Comparator/ Control

The review will compare health utilities reported from patients receiving the treatments listed above at selected treatment time points.

Context

Any setting — inpatient, outpatient, community.

Main outcome

Quality of life health utilities i.e. EQ-5D-3L and EQ-5D-5L at selected treatment time points.

Timing and effect measures

Baseline, 30 days, 6 months (short term), 12-24 months (mid-term), more than 24 months (long term).

Study screening

Yields from searches will be exported into the reference manager software EndNote x9 (www.endnote.com). Duplicates will be removed. Two copies of the EndNote library will be made for two researchers (EL, VM) to independently screen study titles and abstracts against inclusion and exclusion criteria. Any discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached.

Full text records of the included papers from the first round of screening are then retrieved. Studies will be excluded if full text is not available at this stage or not in English.

Next, all full text records retrieved will be independently assessed against the same inclusion and exclusion criteria by two researchers (EL, VM). Reasons for exclusion will be documented. Any

discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached. Study selection will be illustrated as a PRISMA flow diagram.

Risk of bias (quality) assessment

For included studies, we will use the RoB 2 tool to assess risk of bias at the study level in randomised trials and the ROBINS-I tool for non-randomised studies.(21, 22) The RoB 2 tool prompts judgements regarding biases in five domains: bias arising from the randomisation process, those due to derivations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.(21) The ROBINS-I tool covers seven domains: bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.(22)

One researcher (EL) will complete the risk of bias/quality appraisal; a second researcher (VM) will check the assessment for ten percent of the included studies. Any discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached. All studies will be included in the data synthesis; in addition, studies with low risk of bias will also be analysed separately.

Data extraction

Data extraction will be conducted on all studies that are included. We will take the following approaches to data extraction to ensure published estimates are not counted more than once.

- Where there are multiple analyses for the same dataset, we will use only one estimate per subgroup per time point
- We will use the broadest grouping available for each dataset. For example, if a study reports on all patients with bypass surgery and another reports on subgroups of patients with bypass surgery by their obesity status from the same dataset, we will include only the overall bypass surgery utility weights, not the obesity subgroups
- Where a paper provides updated findings (e.g. for a later time point) from a previous published study of the same quality of life data collection, we will only include data for the later time point from the updated analysis

For baseline or time zero utility measurements, we will note when the EQ-5D questionnaire was given to patients.

For each included study, the following data will be extracted:

- Authors
- Publication date
- Country/countries where study was done
- Baseline presentation of patients
- Treatment received e.g. coronary artery bypass graft, percutaneous coronary intervention and type of stent used
- Survey instrument (e.g. EQ-5D, EQ-5D-5L)

- Location of participants (e.g. hospital – inpatient, hospital – outpatient, home)
- Administration mode of survey (e.g. interviewer, self-completion)
- Respondent identity (e.g. self, proxy)
- Language of survey
- Tariff (preference weights) used to generate utility weights from the EQ-5D results
- Mean utility weights reported for each treatment and time point combination
- Standard error or relevant statistics to enable calculation of the standard error i.e. standard deviation and sample size
- Number of participants in the group, mean age, percentage of men and women in the group
- Percentage of participants with diabetes
- Percentage of participants who currently smoke tobacco

Data extraction will be piloted by one researcher (EL) with five studies randomly selected from the included papers. A second researcher (VM) will check the pilot data extraction. Discrepancies will be resolved via discussion. A third researcher (NG) will moderate if discrepancies are not resolved. Subsequently, one researcher will complete data extraction of the remaining studies (EL). A second researcher will check the data extracted for a random ten percent of included papers (VM). Similarly, discrepancies will be resolved via discussion; a third researcher (NG) will moderate if any discrepancies are unresolved.

An Excel spreadsheet will be set up for data extraction.

Strategy for data synthesis

Mean utility weights for individual studies will be combined using random effects model meta-analyses. We will use the R package, metafor,(23) to do this. A model will be run separately for each time point and treatment.

For utility weights following interventional treatments, we will include all studies related to that particular treatment. Each type of interventional procedure will be analysed separately e.g. CABG, PCI without stent (balloon angioplasty), PCI with bare metal stent (PCI-BMS), PCI with drug-eluting stent (PCI-DES), PCI with absorbable stent (PCI-AS).

For re-hospitalisations for acute coronary artery disease, we will use estimates only from studies related to acute presentations. For other re-hospitalisations we will use estimates only from studies not related to acute presentations.

Analysis of subgroups or subsets

Subgroup analysis of patients with diabetes who received CABG, balloon angioplasty, PCI-BMS, PCI-DES, PCI-AS (if any) will be conducted for the same selected time points regarding the EuroQol EQ-5D. Previous studies have demonstrated increased morbidity and/or mortality among people with diabetes who received coronary revascularisation procedures compared to those without diabetes.(24, 25) Hence, the utility value of the quality of life may differ between patients with diabetes and those without.

Type and method of review

Systematic review, Meta-analysis.

Anticipated or actual start date

27 February 2020.

Anticipated completion date

30 June 2020.

Patient and public involvement

No patient or public involvement.

Ethics and dissemination

Ethical approval is not required for systematic review protocols. Results of the review will be disseminated via publication in a peer-reviewed journal. In addition, should the findings of the review warrant a re-examination of current clinical practice, a brief will be prepared and sent to relevant lead agencies in Australia and Singapore e.g. Ministry of Health (Singapore), Department of Health (Australia), Deeble Institute (Australia).

Data deposition and curation

Data extraction tables will be deposited in an open data repository such as the Open Science Framework (https://osf.io/).

Amendments

All amendments to the protocol will be dated, described, accompanied by a rationale, and documented in PROSPERO post-registration.

DISCUSSION

To date, there is only one systematic review of patient reported quality of life focussed on EQ-5D which was published in 2010 by Dyer et al.(14) Given that important clinical studies in the cardiovascular field have since been published, another review is timely.

Our findings will be useful for economic evaluations to determine relative health benefit when comparing treatments. Knowing the health utilities at various treatment time points following different CAD treatments will facilitate cost-effective policy-making, inform clinical guidelines and practice changes. This study will also be useful to other researchers and decision-makers who wish to work on cost-effectiveness analyses for cardiology. In Singapore where this study is being

undertaken, the health utilities estimated by this study will add value to the national longitudinal database of cardiology patients — SingCLOUD,(26) and other disease registries here and elsewhere that have not collected EQ-5D data.

Limitations are that non-English language articles and studies that use other health-related quality of life instruments will be excluded. We chose to focus on EQ-5D generated health utilities as it is the most widely used generic preference-based measure due to its robustness, reliability, and responsiveness across many health conditions and countries.(16) Health utilities derived from different instruments are not interchangeable with the EQ-5D and there are no straightforward methods for translation.(27)

AUTHOR CONTRIBUTIONS

The systematic review was conceptualised by all authors. EL drafted the protocol, which was critically reviewed by VM, NL and NG. All protocol authors read, provided feedback, and approved the final manuscript. Database searches will be completed by EL; articles will be screened for inclusion and exclusion by EL and VM; data extraction will be led by EL. Data analyses will be done by EL and VM, and reviewed by NL and NG. The guarantor of the review is NG.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

No competing interests to declare.

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Reporting checklist for protocol of a systematic review.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1, Title
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, pending PROSPERO registration
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11, Author Contributions
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	10, Amendments
Support			
Sources	#5a	Indicate sources of financial or other support for the review	11, Funding Statement
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a, no funder 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	n/a, no funder or sponsor
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-4, Introduction
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4, Introduction
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	4, Study design 5, Timeframe of searches 6-7, PICO; Context (setting) 5-6, Types of studies; Inclusion and Exclusion criteria
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	4, Databases 5, Timeframe of searches (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	5, Search strategy
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, Study screening 8-9, Data extraction
Study records - 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)	7, Study screening
Study records - 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	8-9, Data extraction
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	7, Interventions 7, Main outcome – Timing 8-9, Data extraction
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7, Main outcome (3, rationale in Introduction)

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	8, Risk of bias assessment
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9, Strategy for data synthesis
Data synthesis	#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 I2, Kendall's τ)	9, Strategy for data synthesis
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9, Analysis of subgroups
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a – quantitative synthesis is applicable
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, Risk of bias assessment
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8, Risk of bias assessment

evidence

BMJ Open

Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis

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Title page

Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Cardiovascular disease is estimated to affect 423 million people globally. It caused 18 million deaths in 2017 and is projected to cost USD$1 trillion by 2030 worldwide. Coronary artery disease (CAD) is the most common type of cardiovascular disease; CAD treatments can affect patients' quality of life. Valuations of quality of life or health utilities are important for economic evaluations to ascertain relative health benefit when comparing treatments, and can be expected to change for individuals over time. The purpose of this systematic review is to estimate the quality of life of CAD patients reported through the EuroQol EQ-5D questionnaire, from short to longer-term time points following different treatments.

Methods and analysis

PubMed, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website will be systematically searched from January 2003 to March 2020. Published, peer-reviewed, English language studies assessing quality of life of CAD patients using the EQ-5D will be included. One researcher will conduct the search; two researchers will independently screen titles and abstracts for potential inclusion. Full texts of potentially eligible studies will be retrieved for a second round of independent screening against inclusion and exclusion criteria by two researchers. The final list of included studies will be assessed for risk of bias using the Rob 2 and ROBINS-I tools for randomized and non-randomized studies, respectively. Data extraction will be done by one researcher, with data extraction for a random 10% of included studies checked by a second researcher. Mean utility weights for individual studies will be combined using random effects model meta-analyses. A model will be run separately for each time point and treatment. Treatment time points of interest include baseline, 30 days, 6 months, 12-24 months, and more than 24 months. Subgroup analysis of patients with diabetes who received interventional treatments — coronary artery bypass graft or percutaneous coronary intervention with or without stents, will be conducted for the same selected time points.

Ethics and dissemination: Ethics approval is not required for systematic reviews. Results of the review will be disseminated via publication in a peer-reviewed journal.

PROSPERO registration number: Pending

Key words:

Coronary artery disease; quality of life; EQ-5D; coronary artery bypass graft; percutaneous coronary intervention.

ARTICLE SUMMARY

Strengths and limitations of this study

- The search strategy is designed to be comprehensive and aligned with the Peer Review of Electronic Search Strategies (PRESS) guidelines.
- We will use PubMed as one of the databases instead of Medline to capture articles not yet indexed with MeSH terms and those released ahead of print.
- A final search will be run just before data synthesis begins to find any new articles that should be included in the analysis, since the search.
- The systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.
- Inclusion of studies that are available as full text and in English only may lead to language bias.

INTRODUCTION

Cardiovascular disease affects 423 million people globally(1) and causes 31% of deaths annually with 18 million deaths in 2017.(2) Cardiovascular disease is projected to cost USD$1 trillion by 2030 in direct healthcare costs, lost productivity due to disability or premature death, and time lost from work.(3) Coronary artery disease (CAD) is the most common type of cardiovascular disease.(4) Patients with CAD are treated with long-term medications, lifestyle modifications, and/or interventional procedures.(5) Commonly used interventional procedures include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) with or without stents.(5)

Individuals living with CAD experience changes in their quality of life.(6-9) CAD treatments can affect quality of life in either a positive or negative direction; and this can be expected to change over a period of time, particularly in the immediate vs. longer-term period post-CABG or PCI.(6, 7) Quality of life estimates as measured by health utilities are important for economic evaluations to determine relative health benefit when comparing treatments.(10) Health utilities are the numerical value reflecting the strength of an individual's preference for specific health-related outcomes, where 0 represents death and 1 represents full health.(10) Together with length of life, health utilities are used to calculate quality-adjusted life years (QALYs).(10) QALYs are used in cost-effectiveness studies to enable direct comparisons between treatment options.(10)

For chronic illnesses such as coronary artery disease, health utilities over time are particularly important so as not to bias estimates of cost-effectiveness toward treatments that show early but unsustained health benefits, and against those which may only show health benefits in the longer-term.(6) However, health utilities over various time points can be logistically challenging and expensive to collect; and estimates need to be as robust as possible given their use in informing medical decision-making and health-related policies. Hence, to reduce research waste and to increase the robustness of utility estimates, systematic reviews and meta-analyses of health utilities from single studies are conducted.

Previous reviews and meta-analyses of health utilities in cardiovascular diseases focussed on either summarising preference weights of various health-related quality of life instruments(11) or in

synthesising the evidence on the validity and reliability of the EQ-5D.(12) Although the 2010 review by Dyer et al. summarised utility scores of the EQ-5D,(12) a number of important studies such as the ORBITA trial have since been published.(13) We will focus on studies that used the EQ-5D to measure health-related quality of life, as it is the most widely used generic preference-based instrument.(14) The EQ-5D is also the preferred instrument for Health Technology Assessments by the UK National Institute for Health and Care Excellence (NICE), and the Zorginstituut Nederland (ZIN).(14, 15)

The aim of this study is to estimate the quality of life of people with CAD quantified by the EQ-5D at selected time points (short-, mid- and longer-term) following the initiation of different treatments. Definitions of terms used are in Box 1.

Box 1. Definitions

- Coronary artery disease: Any one of the following conditions — coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease (INOCA); acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI), myocardial infarction and no obstructive coronary artery disease (MINOCA); silent ischaemia.
- Optimal medical therapy: A combination of evidence-based treatments recommended by clinical guidelines e.g. medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological).
- Interventional procedures: Coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) with — bare metal stent (PCI-BMS), drug-eluting stent (PCI-DES), absorbable stent (PCI-AS) or without stents (balloon angioplasty), carried out in addition to optimal medical therapy.
- Tariff: Preference weight which reflects the preference on different health states of a particular population.

METHODS AND ANALYSIS

Study design

The study protocol has been developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.(16)

Search strategy

Databases

The following databases and sources will be searched: PubMed, Embase (Ovid), Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website.

A previous study demonstrated that to optimize the search when conducting systematic reviews, the following four electronic databases should be searched as a minimum: Medline, Embase, Web of Science, and Google Scholar.(17) We selected PubMed as it has a larger repository than Medline, including additional life sciences journals, citations that are “ahead of print” and those not yet indexed with MeSH terms.(18) We did not select Google Scholar as the search may not be replicable.

Timeframe

The search will encompass the following period: 1 January 2003 to the date of the first search in 2020. Where the search functions of particular databases do not allow day/month/year to be specified, we will use the month and year e.g. January 2003 to March 2020.

The lower date limit of January 2003 was selected as the first commercially available drug-eluting stent was approved by the US Food and Drug Administration in that year.(19) The upper date limit will be the date of the first search conducted (within the second search in the three-step strategy below); and will subsequently be used as the upper date limit when searching the remaining databases. This strategy ensures that the date range for searches is consistent across all databases.

Search strategy

The search aims to find both published and "ahead of print" publications. A three-step strategy will be used.

1. First search (EL): Initial search limited to PubMed only, followed by analysis of text words in the (a) titles and abstracts of retrieved papers (keywords); and (b) index terms used to describe the articles (metadata, tags). Keywords for the initial search: coronary artery disease; EQ-5D; EQ-5D-3L; EQ-5D-5L; EuroQol; treatment. Output: The search string for the systematic review will be constructed (see Supplementary File).
2. Second search (EL): PubMed, Embase (Ovid), Web of Science, the Cochrane Database of Systematic Reviews, and the EuroQol website will then be searched using the search string constructed from the previous step. The yield from this step will be subjected to title and abstract screening for potential inclusion (first screening), followed by retrieval of full text articles, and screening of full text articles for inclusion (second screening).
3. Third search (EL): The reference list of included articles will be manually examined to identify additional studies for inclusion in the systematic review.

Finally, as per good practice, searches will be re-run just before data synthesis to identify any new studies that should be retrieved for inclusion.

Types of studies to be included

All types of studies will be included so long as inclusion criteria are met. Systematic reviews identified from the search will be examined for relevant studies for inclusion.

Inclusion criteria

- Studies which report on quality of life post-treatment for coronary artery disease — coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease (INOCA); acute coronary syndromes i.e. unstable angina, myocardial infarction (STEMI or NSTEMI), myocardial infarction and no obstructive coronary artery disease (MINOCA); silent ischaemia

- Treatments may be pharmacological, non-pharmacological (e.g. lifestyle modifications), or interventional procedures (e.g. coronary artery bypass graft, percutaneous coronary intervention with or without stents)
- Preference based utility values for quality of life using EQ-5D
- Studies reported in English

Exclusion criteria

- Editorials, letters, and conference proceedings
- Study protocols or studies-in-progress e.g. clinical trial registrations
- Studies which reported only EQ-5D Visual Analogue Scale outcomes
- Studies which reported EQ-5D values derived from mapping other measures of health outcomes
- Studies which reported quality of life from other studies, without contributing new data
- Studies which reported on subgroups of a previously reported dataset
- Specific patient groups known to have highly impaired quality of life (to avoid skewing estimates) e.g. studies examining coronary artery disease in people with depression
- For post-treatment estimates, treatment was not specified e.g. did not report the type of stent used
- Studies on enhanced external counter pulsation (EECP) therapy
- Full text article not available

Condition or domain being studied

Quality of life (health utilities) at various treatment time points for coronary artery disease.

Participants/population

Inclusion: Adults (18 years old and above) diagnosed with coronary artery disease using criteria such as the International Classification of Diseases and Related Health Problems (ICD-10).

Exclusion: People under 18 years old. Highly specific patient groups e.g. studies examining coronary artery disease in people with depression

Interventions

Pharmacological, non-pharmacological, and interventional procedures.

Pharmacological interventions are medications used to manage or treat coronary artery disease and/or prevent secondary cardiovascular events, and may include cholesterol-modifying medications (e.g. statins, ezetimibe and PCSK9 inhibitors), antiplatelets, beta blockers, calcium

channel blockers, ranolazine, nitrates, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB).

Non-pharmacological interventions include lifestyle modifications such as smoking cessation, choosing healthy foods, engaging in regular physical activity/exercise, removing excess weight, and reducing stress.

Interventional procedures: Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) with or without stents (e.g. balloon angioplasty). Stents used in PCI may be bare metal stents, drug-eluting stents, absorbable stents, or absorbable drug-eluting stents. Implantable cardioverter defibrillators (ICD) will not be included.

Comparator/ Control

The review will compare health utilities reported from patients receiving the treatments listed above at selected treatment time points.

Context

Any setting — inpatient, outpatient, community.

Main outcome

Quality of life health utilities i.e. EQ-5D-3L and EQ-5D-5L at selected treatment time points.

Timing and effect measures

Baseline, 30 days, 6 months (short term), 12-24 months (mid-term), more than 24 months (long term).

Study screening

Yields from searches will be exported into the reference manager software EndNote x9 (www.endnote.com). Duplicates will be removed. Two copies of the EndNote library will be made for two researchers (EL, VM) to independently screen study titles and abstracts against inclusion and exclusion criteria. Any discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached.

Full text records of the included papers from the first round of screening are then retrieved. Studies will be excluded if full text is not available at this stage or not in English.

Next, all full text records retrieved will be independently assessed against the same inclusion and exclusion criteria by two researchers (EL, VM). Reasons for exclusion will be documented. Any discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached. Study selection will be illustrated as a PRISMA flow diagram.

Risk of bias (quality) assessment

For included studies, we will use the RoB 2 tool to assess risk of bias at the study level in randomised trials and the ROBINS-I tool for non-randomised studies.(20, 21) The RoB 2 tool prompts judgements regarding biases in five domains: bias arising from the randomisation process, those due to derivations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.(20) The ROBINS-I tool covers seven domains: bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.(21)

One researcher (EL) will complete the risk of bias/quality appraisal; a second researcher (VM) will check the assessment for ten percent of the included studies. Any discrepancies will be resolved via discussion; a third researcher (NG) will moderate if consensus is not reached. All studies will be included in the data synthesis; in addition, studies with low risk of bias will also be analysed separately. The risk of bias assessment for all included studies will be reported in a table format showing the overall judgment for each study (Rob 2: low/ high/ some concerns; ROBINS-I: low/ moderate/ serious/ critical).

Data extraction

Data extraction will be conducted on all studies that are included. We will take the following approaches to data extraction to ensure published estimates are not counted more than once.

- Where there are multiple analyses for the same dataset, we will use only one estimate per subgroup per time point
- We will use the broadest grouping available for each dataset. For example, if a study reports on all patients with bypass surgery and another reports on subgroups of patients with bypass surgery by their obesity status from the same dataset, we will include only the overall bypass surgery utility weights, not the obesity subgroups
- Where a paper provides updated findings (e.g. for a later time point) from a previous published study of the same quality of life data collection, we will only include data for the later time point from the updated analysis

For baseline or time zero utility measurements, we will note when the EQ-5D questionnaire was given to patients.

For each included study, the following data will be extracted:

- Authors
- Publication date
- Country/countries where study was done
- Baseline presentation of patients
- Treatment received e.g. coronary artery bypass graft, percutaneous coronary intervention and type of stent used
- Survey instrument (e.g. EQ-5D, EQ-5D-3L, EQ-5D-5L)
- Location of participants (e.g. hospital – inpatient, hospital – outpatient, home)
- Administration mode of survey (e.g. interviewer, self-completion)

- Respondent identity (e.g. self, proxy)
- Language of survey
- Tariff (preference weights) used to generate utility weights from the EQ-5D results
- Mean utility weights reported for each treatment and time point combination
- Standard error or relevant statistics to enable calculation of the standard error i.e. standard deviation and sample size
- Number of participants in the group, mean age, percentage of men and women in the group
- Percentage of participants with diabetes
- Percentage of participants who currently smoke tobacco

Data extraction will be piloted by one researcher (EL) with five studies randomly selected from the included papers. A second researcher (VM) will check the pilot data extraction. Discrepancies will be resolved via discussion. A third researcher (NG) will moderate if discrepancies are not resolved. Subsequently, one researcher will complete data extraction of the remaining studies (EL). A second researcher will check the data extracted for a random ten percent of included papers (VM). Similarly, discrepancies will be resolved via discussion; a third researcher (NG) will moderate if any discrepancies are unresolved.

An Excel spreadsheet will be set up for data extraction.

Strategy for data synthesis

Mean utility weights for individual studies will be combined using random effects model meta-analyses. We will use the R package, metafor,(22) to do this. A model will be run separately for each time point and treatment.

For utility weights following interventional treatments, we will include all studies related to that particular treatment. Each type of interventional procedure will be analysed separately e.g. CABG, PCI without stent (balloon angioplasty), PCI with bare metal stent (PCI-BMS), PCI with drug-eluting stent (PCI-DES), PCI with absorbable stent (PCI-AS).

For re-hospitalisations for acute coronary artery disease, we will use estimates only from studies related to acute presentations. For other re-hospitalisations we will use estimates only from studies not related to acute presentations.

Analysis of subgroups or subsets

Subgroup analysis of patients with diabetes who received CABG, balloon angioplasty, PCI-BMS, PCI-DES, PCI-AS (if any) will be conducted for the same selected time points regarding the EuroQol EQ-5D. Previous studies have demonstrated increased morbidity and/or mortality among people with diabetes who received coronary revascularisation procedures compared to those without diabetes.(23, 24) Hence, the utility value of the quality of life may differ between patients with diabetes and those without.

We will also conduct subgroup analysis of patients with acute coronary syndromes (ACS) vs stable CAD /stable coronary syndromes (SCS). ACS includes unstable angina, NSTEMI, STEMI, myocardial

infarction with no obstructive coronary artery disease (MINOCA); and stable CAD includes obstructive CAD and ischaemia with no obstructive coronary artery disease (INOCA).(25)

Type and method of review

Systematic review, Meta-analysis.

Anticipated or actual start date

27 February 2020.

Anticipated completion date

31 August 2020.

Patient and public involvement

No patient or public involvement.

Ethics and dissemination

Ethical approval is not required for systematic review protocols. Results of the review will be disseminated via publication in a peer-reviewed journal. In addition, should the findings of the review warrant a re-examination of current clinical practice, a brief will be prepared and sent to relevant lead agencies in Australia and Singapore e.g. Ministry of Health (Singapore), Department of Health (Australia), Deeble Institute (Australia).

Data deposition and curation

Data extraction tables will be deposited in an open data repository such as the Open Science Framework (https://osf.io/).

Amendments

All amendments to the protocol will be dated, described, accompanied by a rationale, and documented in PROSPERO post-registration.

DISCUSSION

To date, there is only one systematic review of patient reported quality of life focussed on EQ-5D which was published in 2010 by Dyer et al.(12) Given that important clinical studies in the cardiovascular field have since been published, another review is timely.

Our findings will be useful for economic evaluations to determine relative health benefit when comparing treatments. Knowing the health utilities at various treatment time points following different CAD treatments will facilitate cost-effective policy-making, inform clinical guidelines and practice changes. This study will also be useful to other researchers and decision-makers who wish to work on cost-effectiveness analyses for cardiology. In Singapore where this study is being undertaken, the health utilities estimated by this study will add value to the national longitudinal database of cardiology patients — SingCLOUD,(26) and other disease registries here and elsewhere that have not collected EQ-5D data.

Limitations are that non-English language articles and studies that use other health-related quality of life instruments will be excluded. We chose to focus on EQ-5D generated health utilities as it is the most widely used generic preference-based measure due to its robustness, reliability, and responsiveness across many health conditions and countries.(14) Health utilities derived from different instruments are not interchangeable with the EQ-5D and there are no straightforward methods for translation.(27)

AUTHOR CONTRIBUTIONS

The systematic review was conceptualised by all authors. EL drafted the protocol, which was critically reviewed by VM, NL and NG. All protocol authors read, provided feedback, and approved the final manuscript. Database searches will be completed by EL; articles will be screened for inclusion and exclusion by EL and VM; data extraction will be led by EL. Data analyses will be done by EL and VM, and reviewed by NL and NG. The guarantor of the review is NG.

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COMPETING INTERESTS STATEMENT

No competing interests to declare.

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Supplementary File. PubMed search strategy

#1	((((((((((coronary artery disease) OR (coronary heart disease)) OR (coronary artery stenosis)) OR (cardiovascular disease)) OR (myocardial ischemia)) OR (myocardial infarction)) OR (acute coronary syndrome)) OR (angina)) OR (angina pectoris)) OR (chest pain)) OR (silent ischemia)) OR (myocardial ischemia[MeSH Terms])
#2	((((((((((EQ-5D) OR (EQ-5D-3L)) OR (EQ-5D-5L)) OR (EuroQOL)) OR (European Quality of Life - 5 Dimensions)) OR (European QOL - 5 Dimensions)) OR (EuroQOL five-dimensional questionnaire)) OR (EuroQOL 5D)) OR (Quality of life[MeSH Terms])) OR (Quality-adjusted life years[MeSH Terms])) OR (Cost-benefit analysis[MeSH Terms])
#3	((((((((((((((((((optimal medical treatment) OR (best medical therapy)) OR (coronary revascularization)) OR (myocardial revascularization)) OR (coronary angiography)) OR (coronary artery bypass graft)) OR (CABG)) OR (percutaneous coronary intervention)) OR (PCI)) OR (drug-eluting stent)) OR (Paclitaxel-eluting stent)) OR (Sirolimus-eluting stent)) OR (Everolimus-eluting stent)) OR (bare metal stent)) OR (angioplasty)) OR (myocardial ischemia/drug therapy[MeSH Terms])) OR (myocardial ischemia/surgery[MeSH Terms])) OR (myocardial revascularization[MeSH Terms])) OR (percutaneous coronary intervention[MeSH Terms])) OR (drug-eluting stent[MeSH Terms])
#4	((#1) AND (#2)) AND (#3)
#5	((((#4) NOT (stroke[MeSH Terms])) NOT (peripheral arterial disease[MeSH Terms])) NOT (venous insufficiency[MeSH Terms])) NOT (atherectomy[MeSH Terms])
#6	(((#5) NOT (editorial[Publication Type])) NOT (clinical conference[Publication Type])) NOT (letter[Publication Type])
#7	(#6) AND (English[Language])
#8	(#7) AND (("2003/01/01"[Date - Entry] : "2020/03/09"[Date - Entry]))

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1, Title
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a, not an update

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, pending PROSPERO registration
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11, Author Contributions
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	10, Amendments
Support			
Sources	#5a	Indicate sources of financial or other support for the review	11, Funding Statement
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a, no funder 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	n/a, no funder or sponsor
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-4, Introduction
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4, Introduction
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	4, Study design 5, Timeframe of searches 6-7, PICO; Context (setting) 5-6, Types of studies; Inclusion and Exclusion criteria
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	4, Databases 5, Timeframe of searches (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	5, Search strategy and Supplementary File
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, Study screening 8-9, Data extraction
Study records - 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)	7, Study screening
Study records - 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	8-9, Data extraction
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	6-7, Interventions 7, Main outcome – Timing 8-9, Data extraction
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7, Main outcome (3, rationale in Introduction)

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	8, Risk of bias assessment
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9, Strategy for data synthesis
Data synthesis	#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 I2, Kendall's τ)	9, Strategy for data synthesis
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9, Analysis of subgroups
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a – quantitative synthesis is applicable
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, Risk of bias assessment
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8, Risk of bias assessment

evidence