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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 US$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 patients with CAD reported through the EuroQol 5 Dimension (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–March 2020. Published, peer-reviewed, English language studies assessing quality of life of patients with CAD 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 Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tools for randomised and non-randomised 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.

Strengths and limitations of this study

► The search strategy is designed to be comprehensive and aligned with the Peer Review of Electronic Search Strategies guidelines.

► We will use PubMed as one of the databases instead of Medline to capture articles not yet indexed with Medical Subject Headings (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 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 US$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 versus 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 CAD, health utilities over time are particularly important so as not to bias estimates of cost effectiveness towards 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 focused 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 EuroQol 5 Dimension (EQ-5D) instrument.[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 Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (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, and the Zorginstituut Nederland.[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 terms) following the initiation of different treatments. Definitions of terms used are in box 1.

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.

> **Box 1   Definitions**
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> ► Coronary artery disease: any one of the following conditions—coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease; acute coronary syndromes, that is, unstable angina, myocardial infarction (ST-elevation myocardial infarction or non-ST-elevation myocardial infarction), myocardial infarction and no obstructive coronary artery disease; silent ischaemia.
> ► Optimal medical therapy: a combination of evidence-based treatments recommended by clinical guidelines, for example, medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological).
> ► Interventional procedures: coronary artery bypass graft, percutaneous coronary intervention with—bare metal stent, drug-eluting stent, absorbable stent 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.

A previous study demonstrated that to optimise 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 Medical Subject Headings (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, for example, January 2003–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 online 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 rerun 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 CAD—coronary atherosclerosis, angina, ischaemia and no obstructive coronary artery disease (INOCA); acute coronary syndromes (ACS), that is, unstable angina, myocardial infarction (ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI)), myocardial infarction and no obstructive coronary artery disease (MINOCA); silent ischaemia.

► Treatments may be pharmacological, non-pharmacological (eg, lifestyle modifications), or interventional procedures (eg, CABG, PCI 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, for example, 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), for example, studies examining CAD in people with depression.

► For post-treatment estimates, treatment was not specified, for example, did not report the type of stent used.

► Studies on enhanced external counter pulsation therapy.

► Full-text article not available.

Condition or domain being studied

Quality of life (health utilities) at various treatment time points for CAD.

Participants/population

Inclusion: adults (18 years old and above) diagnosed with CAD 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, for example, studies examining CAD in people with depression.

Interventions

Pharmacological, non-pharmacological, and interventional procedures.

Pharmacological interventions are medications used to manage or treat CAD and/or prevent secondary cardiovascular events, and may include cholesterol-modifying medications (eg, statins, ezetimibe and PCSK9 inhibitors), antiplatelets, beta blockers, calcium channel blockers, ranolazine, nitrates, ACE inhibitors, angiotensin II receptor blockers.

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: CABG or PCI with or without stents (eg, 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, that is, 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 V.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 Risk Of Bias In Non-randomized Studies - of Interventions (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 10% of the included studies. Any discrepancies will be resolved via discussion; a third researcher (NG) will be 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 judgement 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 (eg, 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, for example, CABG, PCI and type of stent used.
► Survey instrument (eg, EQ-5D, EQ-5D-3L, EQ-5D-5L).
► Location of participants (eg, hospital—inpatient, hospital—outpatient, home).
► Administration mode of survey (eg, interviewer, self-completion).
► Respondent identity (eg, 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.
► SE or relevant statistics to enable calculation of the SE, that is, SD 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 10% 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, for example, CABG, PCI without stent (balloon angioplasty), PCI with bare metal stent (PCI-BMS), PCI with drug-eluting stent (PCI-DES) and PCI with absorbable stent (PCI-AS).

For rehospitalisations for acute CAD, we will use estimates only from studies related to acute presentations.

For other rehospitalisations, 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 and PCI-AS (if any) will be conducted for the same selected time points regarding the EQ-5D. Previous studies have demonstrated increased morbidity and/or mortality among people with diabetes who received coronary revascularisation procedures compared with 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 ACS versus stable CAD/stable coronary syndromes. ACS includes unstable angina, NSTEMI, STEMI, MINOCA; and stable CAD includes obstructive CAD and 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, for example, 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 the International Prospective Register of Systematic Reviews (PROSPERO) post registration.

DISCUSSION

To date, there is only one systematic review of patient reported quality of life focused 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]

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REFERENCES

1 Roth GA, Johnson C, Abajobir A, *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;70:1–25.

2 Mensah GA, Roth GA, Fuster V. The Global Burden of Cardiovascular Diseases and Risk Factors: 2020 and Beyond. *J Am Coll Cardiol* 2019;74:2529–32.

3 Bloom D, Cafiero E, Jane-Llopis E, *et al*. *The global economic burden of non-communicable diseases*. Geneva: World Economic Forum, 2011.

4 Centers for Disease Control and Prevention. Heart disease facts, 2019. Available: https://www.cdc.gov/heartdisease/facts.htm

5 NIH National Heart Lung and Blood Institute. Coronary heart disease, 2020. Available: https://www.nhlbi.nih.gov/health-topics/coronary-heart-disease

6 Sajobi TT, Wang M, Awosoga O, *et al*. Trajectories of health-related quality of life in coronary artery disease. *Circ Cardiovasc Qual Outcomes* 2018;11:e003661.

7 Yang L-X, Zhou Y-J, Wang Z-J, *et al*. Impact of invasive treatment strategy on health-related quality of life six months after non-ST-elevation acute coronary syndrome. *J Geriatr Cardiol* 2014;11:206–11.

8 Sipötz J, Friedrich O, Höfer S, *et al*. Health related quality of life and mental distress after PCI: restoring a state of equilibrium. *Health Qual Life Outcomes* 2013;11:144.

9 Gencer B, Girardin F. Coronary artery disease is associated with persistent lower quality of life in women. *Open Heart* 2015;2:e000305.

10 Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010;96:5–21.

11 Stevanović J, Pechlivanoglou P, Kampinga MA, *et al*. Multivariate meta-analysis of Preference-Based quality of life values in coronary heart disease. *PLoS One* 2016;11:e0152030.

12 Dyer MTD, Goldsmith KA, Sharples LS, *et al*. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;8:13.

13 Al-Lamee R, Thompson D, Dehbi H-M, *et al*. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31–40.

14 Brazier JE, Rowen D, Lloyd A, *et al*. Future directions in Valuing benefits for estimating QALYs: is time up for the EQ-5D? *Value Health* 2019;22:62–8.

15 National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England, 2019.

Available: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l

16 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

17 Bramer WM, Rethlefsen ML, Kleijnen J, *et al*. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev* 2017;6:245.

18 NIH National Library of Medicine. MEDLINE, PubMed, and PMC (PubMed central): how are they different? 2019. Available: https://www.nlm.nih.gov/bsd/difference.html

19 Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. *Br Med Bull* 2013;106:193–211.

20 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

21 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.

22 Viechtbauer W. Conducting Meta-Analyses in *R* with the metafor Package. *J Stat Softw* 2010;36:1–48.

23 Armstrong EJ, Waltenberger J, Rogers JH. Percutaneous coronary intervention in patients with diabetes: current concepts and future directions. *J Diabetes Sci Technol* 2014;8:581–9.

24 Kereiakes DJ. Percutaneous coronary intervention in diabetic patients – improving outcomes through advances in Catheter-based and adjunctive pharmacotherapeutic strategies. *Interventional Cardiology* 2008;3:33–6.

25 Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart* 2018;104:284.

26 Yeo KK, Ong H-Y, Chua T, *et al*. Building a Longitudinal National Integrated Cardiovascular Database   — Lessons Learnt From SingCLOUD —. *Circ Rep* 2020;2:33–43.

27 Longworth L, Rowen D. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. *Value Health* 2013;16:202–10.