**Suppl 9.**

**Does estimated glomerular filtration rate influence receipt of coronary intervention following myocardial infarction? A protocol for a systematic review.**

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**Background**

Myocardial infarction (MI) is a major cause of mortality and morbidity amongst people with chronic kidney disease (CKD). The incidence of myocardial infarction (MI) in people with CKD is up to four-fold that in the general population(1), due to increased prevalence of traditional cardiovascular risk factors in addition to risk factors specific to the pro-inflammatory and uraemic milieu of kidney disease(2). MI and other cardiovascular diseases are the most common cause of death in those with CKD(3). Death from cardiovascular disease is more common than progression to end-stage kidney disease in those with moderate (stage 3) CKD(4).

People with CKD experience worse outcomes after MI than those without kidney disease(5-7). Progressively worse outcomes are seen with increasing CKD severity such that a 10 ml/min decrease in creatinine clearance was found to have an equivalent impact on risk of mortality as a 10 year increase in age(8). Kidney disease is associated with prolonged hospital admission, lower likelihood of return to work and increased risk of recurrent MI(9). Our understanding of the pathophysiology and optimal management strategies for MI in people with CKD is however limited, as those with moderate to severe CKD (stage 3-5) have been systematically excluded from the majority of randomised controlled trials that have advanced our knowledge and treatment of MI in the general population(10).

Coronary artery revascularisation improves survival and quality of life after MI(16). Revascularisation improves blood supply to ischaemic myocardium, improving symptoms of angina, and reducing risk of recurrent MI and cardiovascular mortality. Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) offer different advantages and disadvantages. Compared with PCI, CABG is associated with increased risk of stroke, acute Kidney injury (ACKD) and mortality during hospitalisation, with lower rates of recurrent MI, further revascularisation procedures and death in the longer-term. Choice of revascularisation strategy depends on numerous factors such as anatomic complexity, comorbidities and patient preferences(50).

The Syntax scores (I and II) have been developed to estimate relative mortality differences associated with CABG versus PCI for individual patients(20, 51). The score takes into account coronary anatomy, patient demographics and comorbidities including kidney function. Reduced kidney function increases the predicted benefit from CABG over PCI. Clinicians may opt to avoid CABG in people with kidney disease however, in view of technical challenges related to diffuse vessel calcification, in addition to increased post-operative morbidity and mortality related to both the kidney disease and associated frailty.(21, 22, 52). It is unknown therefore, whether Syntax scoring translates into clinical practice for this population.

CKD may influence clinical decision-making at multiple stages during the treatment pathway for MI due to concerns regarding contrast nephropathy, vascular access and relative mortality benefit. Observational studies suggest that people with CKD may be less likely to be managed invasively following an MI than those with normal Kidney function(5, 7, 11). To our knowledge, rates of invasive management have not previously been systematically compared between the CKD and non-CKD populations.

The aim of this systematic review is to determine whether receipt of CABG versus PCI differs amongst people with and without reduced estimated glomerular filtration rate (eGFR) who undergo coronary revascularisation following an MI. We will also examine whether receipt of the precursor steps i) coronary angiography and ii) revascularisation (any) differ between people with and without reduced eGFR.

**Objectives**

The objectives of this systematic review are to assess whether eGFR affects the receipt of coronary artery intervention following myocardial infarction.

**Definitions**

**The following definitions apply to this review:**

1. Reduced eGFR will be defined as:
* A clinical code indicating CKD (stage unspecified) or CKD stage 3-5 (during index inpatient admission or in prior two years).
* One or more eGFR values <60mls/min/1.73m2 within three days of MI.
* A clinical code indicating receipt of haemodialysis, haemodiafiltration or peritoneal dialysis for Kidney failure (during index inpatient admission or in prior two years).
1. Normal eGFR will be defined as:
* A clinical code indicating CKD stage 1-2 (during index inpatient admission or in prior two years).
* Absence of a clinical code indicating CKD stage 3-5 or receipt of haemodialysis, haemodiafiltration or peritoneal dialysis (during index inpatient admission or in prior two years).
* One or more eGFR values ≥60mls/min/1.73m2 within three days of MI.
* Where an individual has eGFR values (or creatinine values consistent with an eGFR of) ≥60 and <60mls/min/1.73m2 within three days of MI, the Kidney function measure closest in time to the index MI event will be taken as the exposure
1. MI will be defined as a clinical diagnosis of type 1 myocardial infarction (either subendocardial or transmural). Where the type of myocardial infarction is not specified, it will be assumed to be type 1.
2. Coronary revascularisation will be defined as:
	1. Percutaneous coronary intervention (PCI)
	2. Coronary artery bypass graft (CABG)
	3. Thrombolysis
3. Medical management will be defined as the treatment received by any patient who is hospitalized for MI and does not receive any form of coronary artery revascularization (i.e. PCI, CABG or thrombolysis)

**Methods**

This protocol is structured according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidance.(53)

**Eligibility criteria**

Studies will be eligible for inclusion in the systematic review if they meet the following criteria.

***Study design***

Eligible study designs will include observational studies; cross-sectional studies, case-control studies, retrospective and prospective cohort studies, case series (reporting on more than ten individuals), other observational studies and mixed-methods studies. For mixed-methods studies, only the quantitative data will be extracted and reviewed. Systematic reviews and meta-analyses will be included up to, and including the stage of screening, in order that we can ensure that we have included any relevant individual studies that they reference. Case reports, small case series (less than ten individuals), clinical trials and qualitative studies will be excluded.

***Population***

Studies must include adult humans ≥18 years of age with a clinical diagnosis of MI.

***Exposure***

Eligible studies will investigate outcomes in people with reduced eGFR, defined as any of the following:

* A clinical code indicating CKD (stage unspecified) or CKD stage 3-5 (during index inpatient admission or in prior two years).
* One or more eGFR values <60mls/min/1.73m2 within three days of MI.
* A clinical code indicating receipt of haemodialysis, haemodiafiltration or peritoneal dialysis for Kidney failure (during index inpatient admission or in prior two years).

Studies involving patients with acute Kidney injury (only), will be excluded. People with a functioning Kidney transplant will be excluded.

Eligible studies will have a comparator population with normal eGFR (see prior definition).

***Outcomes***

Primary outcome:

* Odds of CABG amongst people with reduced eGFR who are revascularized following an MI, compared to people with normal eGFR.

Secondary outcomes:

* Odds of revascularization (any) following an MI in people with versus without reduced eGFR.
* Odds of coronary angiography following an MI in people with versus without reduced eGFR.

For all outcomes, the relative odds of the outcome in the exposed versus unexposed populations will be described for both a potential observational and a potential causal association. In the latter, confounding variables will be taken into account.

***Setting***

Studies carried out in secondary or tertiary healthcare facilities in any high income country will be considered. Low and middle income countries will not be covered in this review as financial constraints are likely to influence rates of coronary artery intervention following MI.

***Language***

Eligible studies written in any language will be included if the abstract is available in English.

***Timeframe and publication status***

Studies eligible for inclusion will be written between 2012 and May 2022. Both published studies and grey literature will be considered.

**Information sources**

The following databases will be searched to identify eligible studies: MEDLINE (Ovid), EMBASE, Scopus, and CENTRAL, the NIHR’s website of funded studies. The charitable organisations Kidney Research UK and the British Heart Foundation will be contacted and asked for information on unpublished and ongoing studies that may be relevant to this review. Reference lists of included studies will be reviewed to identify any further studies meeting the eligibility criteria. Systematic reviews and meta-analyses will be included up to the screening stage, as an additional check that studies included therewithin have been identified from the wider search strategy.

**Search strategy**

The specific search strategy was developed using a combination of medical subject headings (for MEDLINE and CENTRAL), Emtree terms (for EMBASE) and free text words. Experienced Health Sciences Librarians at the University of Bristol assisted in the development of the search strategies.

The search strategy framework will include terms relating to MI and those relating to invasive coronary artery imaging and intervention (coronary angiography, coronary artery revascularisation (any), PCI, CABG).

The example search strategies for Medline (Ovid) are included in Appendix 1.

The latest search was run on 19th April 2022 for Medline, Embase and Central, and 21st April for Scopus. The searches will be re-run if more than 12 months pass between the latest search and publication, and additional papers included in the discussion.

**Study records**

***Data management***

Citations and abstracts for studies identified during the search process will be uploaded to EndNote referencing software and duplicate studies removed. Results will then be transferred to an appropriate software package. Articles not written in English will be translated either by voluntary assistance through the Cochrane TaskExchange platform,(54) or alternatively via google translate. Following screening of the titles and abstracts, full texts for all studies identified as either definitely or potentially eligible, will be uploaded.

***Selection process***

Titles and abstracts of the studies identified during the search process will be screened against pre-defined eligibility criteria defined in the abstract screening tool (Appendix 2). Studies will be screened by one of four authors (JS, ML, CC, WHA). JS is a research fellow and clinical trainee in renal medicine. ML, CC and WHA are a clinical trainees. The abstract screening tool will initially be piloted against 25 abstracts to ensure consistency between authors as well as clarity. Changes to the tool will be avoided, but if necessary, these will be documented and the protocol amended. Abstracts designed ineligible for inclusion by will be discarded.

Full texts for any study determined to be eligible, or potentially eligible for inclusion by one or more authors will be uploaded to Rayyan. Non-identical reports on any single study will be collated and the review written with respect to the study rather than any single report. Full-texts will be reviewed against the inclusion and exclusion criteria to determine their eligibility. Texts that are deemed of unclear eligibility will be reviewed by a second author, and a decision made by discussion between the two authors. Further information will be requested from study authors where required to make an assessment about eligibility; the corresponding author will be contacted twice be email two weeks apart. Studies that are ongoing or unobtainable will be tagged and recorded. The selection process will be documented and published in a flow diagram. The key characteristics of excluded studies and the reason for exclusion will be recorded and subsequently published.

Reference lists from all eligible full texts will be reviewed to identify further studies meeting the inclusion criteria that may not have been identified at the stage of literature search.

***Data collection***

A data collection form will be created using Excel. The four authors will pilot the form using 10-20% of selected texts to determine the completeness and clarity of questions, and the accuracy of extracted data. Further piloting will be undertaken if significant changes to the data collection form are required following initial assessment. The four authors will then independently extract data from the remainder of included studies. If multiple reports are identified relating to a single study, these will initially be recorded in the data collection form a) separately, if they each relate to the full study or b) combined, if only one is a report of the full study and the other(s) abstract(s). The reports will subsequently be combined. Differences in reports of a single study will be resolved by contacting the study’s authors.

Uncertainty in data extraction will be resolved by discussion with a further author and/or by requesting further information from study authors as required. Where disagreements cannot be resolved in this way, a third author will be consulted. This process will be documented by maintaining the original data collection forms, and creating a final consensus form in addition.

The data collection form will include the following:

**Information about data extraction**

* Name of the data extractor
* Date of data extraction

**Study details**

* Name of study
* Location of study publication
* Study author(s)
* Publication date

**Eligibility criteria**

* Eligibility of the study for review
* Reason for exclusion (as applicable)

**Study design**

* Type of study
* Single or multicentre study
* Recruitment and sampling procedure
* Study start and end date
* Length of participant follow-up
* Number of exposure groups in relation to CKD
* Statistical analysis
	+ Sample size (if reported)
	+ Statistical methods (including attempt to adjust for confounders)
	+ Likelihood of reporting
* Primary outcome
* Other outcomes
* Source of funding
* Authors’ conflicts of interest

**Participants**

* Healthcare setting
* Country from where participants were recruited/observed
* Study eligibility criteria (including diagnostic criteria)
* Characteristics of participants (eg age, sex, ethnicity, comorbidities)
* Specific clinical scenario (where relevant)
* Definition of exposure (reduced eGFR)
* Datasource used to define exposure
* Timeframe for definition of exposure
* Definition of MI
* Attempt to exclude type two myocardial infarction

**Duration of follow-up**

**Result(s)**

* Summary statistics relevant to exposure
* Absolute number of people with and without reduced eGFR receiving:
	+ Coronary angiography
	+ Revascularisation (any)
	+ CABG
* Effect estimate for the receipt of invasive management in people with versus without reduced eGFR (normal eGFR as the comparator). Effect estimates for:
	+ Coronary angiography
	+ Revascularisation (any)
	+ CABG
* Type of effect estimate
* Confounders adjusted for (where relevant)

**Miscellaneous**

* Key conclusions of study authors
* Reference to other relevant studies
* Correspondence required
* Other

**Outcomes**

Outcome 1: Receipt of CABG in people with versus without reduced eGFR undergoing revascularisation following MI

Outcome 3: Receipt of revascularisation (any) versus medical management (only) in people with versus without reduced eGFR following MI.

Outcome 3: Receipt of coronary angiography in people with versus without reduced eGFR following MI

**Risk of bias assessment**

Two authors (JS and ML) will independently assess the risk of bias in included studies using the ROBINS-I tool for nonrandomised studies and the Cochrane Risk of Bias (RoB) tool for randomised trials.(55) (56) Each author will record their risk of bias assessment within each domain, as well as an overall judgement as to whether the study is of sufficient quality to be included in the review. This data will be presented as a table in supplementary material. Where risk of bias is unclear, the study author will be contacted in the first instance. Disagreements between authors will be resolved by discussion, or if necessary, involvement of a third author.

**Data synthesis**

The PEO characteristics of each study will be summarised and reported in a “characteristics of included studies” table. If there is significant variation in terminology across studies, this will be standardised. Clinical and methodological characteristics will be compared across studies, including study type, date of study, exposure definition, type of outcome data (time to diagnosis or treatment) and risk of bias. Characteristics will be compared across studies to determine which studies are sufficiently similar to be grouped together for analysis. Depending on the data available, modifications to the planned comparisons or outcomes may be made, or new comparisons determined. Any changes to the original protocol will be documented.

A decision will be made as to whether the studies are sufficiently similar that a statistical synthesis can be performed. If this is not possible, studies will be compared against one another in a narrative synthesis. Summary tables and text will be used to describe the studies included, and conclusions drawn regarding the overall body of information.

In the event that the included studies (or a subset of studies) are sufficiently homogeneous with respect to key characteristics (for example, participants and type of outcome data), meta-analysis will be considered. The I2 statistic will be calculated to quantify the impact of inconsistency between studies on the results of the meta-analysis.(57) If the I2 is greater than 50%, the data will be rechecked to ensure that it is correct and the effect measure re-considered to ensure that it is appropriate. If the data is correct and there is inconsistency in the direction of the effect, a meta-analysis will not be undertaken. If there is a single direction of effect is identified, a random-effects meta-analysis will be performed. If the I2 is less than 50% with a unified direction of effect, a fixed effect meta-analysis will be undertaken using the Mantel-Haenszel method.(58) Data analysis will be undertaken within STATA 17.

**Subgroup analyses**

1. Rates of coronary intervention before and after the routine introduction of primary PCI (2009).

2. Rates of coronary intervention before versus during the COVID pandemic

3. Rates of coronary intervention in STEAC versus NSTEAC

4. Rates of coronary intervention by degree of reduction in eGFR

**Meta-bias(es)**

Missing results can introduce significant bias into a systematic review or meta-analysis.(59, 60) The following steps will be undertaken to avoid this. Firstly, multiple data sources will be used to identify studies eligible for inclusion into this review, including review of the reference lists for all included studies and contacting key research charities in the fields of cardiac and renal medicine. Secondly, selective non-reporting or under-reporting of results will be assessed by comparing the results of all studies with their protocols (where available).

If the protocol is unavailable, or there is a suspicion that results may be unavailable due to their P-value, magnitude or direction, the study author will be contacted twice by email in an attempt to access these data. Failure to obtain the results requested will be acknowledged when discussing the limitations of the review process. The ORBIT system will be used to determine whether such results are likely to be unavailable due to their P-value, magnitude or direction of results.(61) Suspected outcome reporting bias will be taken into account when assessing the overall quality of evidence using GRADE.(24) Publication bias will be assessed by reviewing funnel plot asymmetry with Egger’s test.(62)

**Confidence in cumulative evidence**

Tables reporting the “summary of findings” will be generated for each comparison, using GRADE’s software GRADEpro GDT. The GRADE approach will be used to assess the quality of evidence with respect to risk of bias, consistency, precision, directness and probability of reporting bias.(24)

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