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Late myocardial reperfusion in ST-elevation myocardial infarction: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction ST-segment elevation myocardial infarction (STEMI) is the most severe clinical form of acute myocardial infarction, for which the current treatment consists of effective and timely myocardial reperfusion (within 12 hours of symptom onset). However, between 10% and 15% of patients with STEMI arrive at hospital facilities 12 hours after the onset of symptoms (late presentation). Therefore, the objective of the present study will be to determine if late revascularisation (12–72 hours after the onset of symptoms) affects the indicators of cardiovascular mortality, reinfarction, recurrent infarction, hospitalisation for heart failure and post infarction angina compared with no late revascularisation in patients with STEMI.

Methods and analysis A systematic literature search of PubMed, The Cochrane Library, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus and Global Health will be conducted. Publications in English, Portuguese or Spanish that report the clinical results of primary percutaneous revascularisation (primary PCI) in adult patients with STEMI 12–72 hours after the onset of symptoms will be included. Studies with participants with a diagnosis other than STEMI or patients with STEMI of >12 hours complicated by heart failure, cardiogenic shock or ventricular arrhythmias, and studies of combined interventions (pharmacoinvasive strategy) were excluded. Two independent authors will identify the relevant publications, and discrepancies will be adjudicated by a third author. Data extraction will be performed by two independent authors and verified by a third author. Risk of bias of studies will be assessed using the Cochrane 'risk of bias' tool (RoB 2) or Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. If appropriate, a meta-analysis will be performed in order to examine the effect of late revascularisation in clinical outcomes of interest.

Ethics and discussion This study will use published data only, thus, ethical approval will not be required. The results will be disseminated through peer-reviewed publication and conference presentations.

PROSPERO registration number CRD42021283429.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines.
⇒ The search strategies were developed by an experienced librarian in systematic reviews and will use bibliographic databases that are recommended for studies of interventions.
⇒ By not taking grey literature into account in the search, we could exclude studies that would be of relevance for the systematic review.
⇒ The heterogeneity of the studies due to differences in population, study design and intervention could prevent the meta-analysis from being carried out.
⇒ Subgroup analysis and quality of the evidence using Grading of Recommendations, Assessment, Development and Evaluation will be considered where possible.

INTRODUCTION

Cardiovascular diseases (CVD) are one of the main causes of morbidity and mortality around the world.[1] It is estimated that 523 million people worldwide had CVD in 2019 (252 million more compared with 1990), generating more than 18 million deaths, and a significant increase in disability-adjusted life years (DALYs) and years of lives lost from 17.7 million in 1990 to over 34 million in 2019.[1] Among CVD, acute myocardial infarction (AMI) is the most prevalent (with more than 195 million cases in 2019), and has generated more than nine million deaths (being the leading cause of death worldwide), and more than 182 million DALYs in 2019.[1]

Regarding the presentation of AMI, ST-segment elevation myocardial infarction (STEMI) is the most severe clinical form of AMI and results from total occlusion of an epicardial artery, usually due to a thrombus on a complicated atherosclerotic plaque.[2] The clinical picture that characterises STEMI is anginal chest pain and ST-segment elevation of 1 mm in two

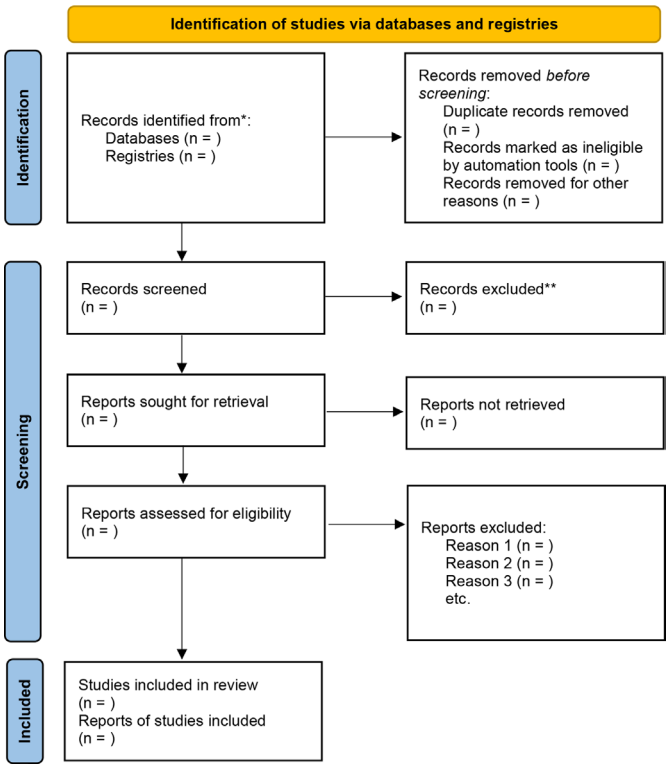

Figure 1 Flow chart of the literature search and study selection. Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

contiguous leads, except for leads V2 and V3, in which it must be greater than or equal to 2 mm in the electrocardiogram in men over 40 years of age, greater than or equal to 2.5 mm in men under 40 years of age and 1.5 mm or more in women.[2 3] STEMI is a high-risk medical emergency that generates high morbidity and mortality, with an incidence of 43–144 cases per 100 000 inhabitants per year and in-hospital mortality between 3% and 13.5% in European countries,[4] while in the United States of America, the incidence is approximately 50 cases per 100 000 inhabitants, with an in-hospital mortality of 5%–18% per year.[5] These figures show that STEMI cases vary according to geographical regions, making this pathology a global health problem.

The current treatment of STEMI consists of effective and timely reperfusion (within 12 hours of onset of symptoms) of the myocardium by restoring blood flow to the occluded coronary artery, generating a decrease in mortality in recent decades.[2 6] However, timely use of reperfusion in patients with STEMI varies among regions,[5 7] and ineffectiveness of care systems, a shortage of trained medical personnel, lack of adequately equipped emergency medical services will not allow timely reperfusion in patients with STEMI.[4 8 9] In addition to these limitations, it is estimated that between 10% and 15% of patients with STEMI arrive at hospital facilities 12 hours after the onset of symptoms (late presentation).[10 11] This subgroup of patients is a challenge for health systems, due to the fact that they have a higher number of complications and a higher in-hospital mortality compared with patients admitted within 12 hours after symptom onset.[10]

On the other hand, while there are clinical practice guidelines that recommend the use of revascularisation in patients who present late to hospital centres,[4 8] the evidence supporting these recommendations is limited, and there is still little scientific evidence on the benefits of late reperfusion in this subgroup of patients. Therefore, the objective of the present study will be to determine if late revascularisation (12 hours after the onset of symptoms) affects the indicators of cardiovascular mortality, reinfarction (within the first 28 days after the index infarction), recurrent infarction (after 28 days), hospitalisation for heart failure, heart failure and unfavourable outcomes in patients with STEMI.

MATERIALS AND METHODS

The protocol was designed according to the extension of the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analysis to inform systematic review protocols (PRISMA-P).[12] The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) with the identification number CRD42021283429. In case of making any changes to this protocol, the registration information in PROSPERO will be updated in a timely manner.

The PRISMA 2020 flow chart will be used to record each step of the review process (figure 1).[13] The review will begin in October 2021 and will be completed by February 2022 at the latest.

Research question

Among patients with STEMI, does late revascularisation affect cardiovascular mortality, reinfarct (within the first 28 days after the index infarction), recurrent infarct (after 28 days), heart failure hospitalisation, cardiac insufficiency and the appearance of unfavourable outcomes compared with non-revascularisation?

Eligibility criteria

Studies to be included will be randomised controlled trials (RCTs), non-RCTs, and comparative observational studies (prospective or retrospective studies). The selection criteria will include studies evaluating adult patients (≥18 years of age) with STEMI undergoing primary percutaneous revascularisation (primary percutaneous coronary intervention [PCI]) beyond 12 hours of symptom onset and reporting at least one of the primary or secondary results published in English, Portuguese, or Spanish, while studies with participants with a diagnosis other than STEMI or patients with STEMI of more than 12 hours complicated by heart failure, cardiogenic shock or ventricular arrhythmias, as well as cross-sectional studies,

case series, case reports, systematic reviews, conference proceedings and editorials will be excluded.

Type of participants

Patients with a diagnosis of STEMI who attended a health facility or had primary PCI between 12 to 72 hours from symptoms' onset.

Type of interventions and comparisons

All studies comparing revascularisation with PCI with no treatment, usual care (post-revascularisation guided by imaging studies for viability or myocardial ischemia) or any other treatment in patients with STEMI beyond 12 hours and before 72 hours after the onset of symptoms will be included.

Studies of combined interventions before and during revascularisation will be excluded because it can be difficult to attribute any effect to the interventional intervention. Studies with patients undergoing a pharmacoinvasive strategy, in which the initial treatment (fibrinolysis) is applied before 12 hours, and coronary intervention between 3 and 24 hours later (more than 12 hours after the onset of symptoms) will also be excluded.

Types of outcome measures

At least one of the following outcomes must have been reported in the study.

Main outcome(s)

- In-hospital cardiovascular mortality
- One-year cardiovascular mortality

Secondary outcome(s)

- Reinfarct (within the first 28 days after the index infarction), recurrent infarct (after 28 days), rehospitalisation due to heart failure, stroke, major bleeding (The thrombolysis in myocardial infarction (TIMI) risk score), and post-infarction angina.

Information sources

Studies will be identified by searching electronic databases from inception to the time of data collection. The electronic databases will include PubMed, The Cochrane Library, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus and Global Health. We will also review the reference lists of each study entering the full-text selection and relevant reviews for additional relevant articles.

Search strategy

The search strategy will be carried out by an experienced medical research librarian (DC) and validated by the research team. The search strategy will be designed using Medical Subject Headings (MeSH) terms and related terms together with Boolean operators in the PubMed bibliographic database and will be adjusted for the other databases. The strategy will be broad, without restrictions by type of study, year of publication or language. The search strategy for PubMed is shown in table 1, and the other strategies are described in the Online Supplementary Material (online supplemental material 1).

Table 1 Search strategy for PubMed

Search line	Search terms
#22	#7 AND #15 AND #21
#21	#16 OR #17 OR #18 OR #19 OR #20
#20	Myocardial Salvage*[tiab]
#19	Myocardium Salvage*[tiab]
#18	Revasculari*[tiab]
#17	Reperfusion*[tiab]
#16	Myocardial Reperfusion[Mesh]
#15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#14	Symptom Onset[tiab]
#13	Delayed Comer*[tiab]
#12	Delayed Present*[tiab]
#11	Late-STEMI[tiab]
#10	Late Comer*[tiab]
#9	Latecomer*[tiab]
#8	Late Present*[tiab]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#6	Myocardial Infarct*[tiab]
#5	ST Segment[tiab]
#4	ST Elevated[tiab]
#3	Elevation Myocardial[tiab]
#2	STEMI[tiab]
#1	ST Elevation Myocardial Infarction[Mesh]

Selection of studies

Registries from all the databases will be exported to EndNote X9 to eliminate duplicate publications following the methodology described by Bramer *et al*.[13] We will record the selection process in sufficient detail to complete a PRISMA 2020 flow diagram. The article selection process will be carried out with the application of the Rayyan web tool.[14]

The selection of studies will consist of two phases. In the first phase, two review authors (FAB-L and GWB-M) will independently assess the titles and abstracts of all the registries identified in the search and that meet the inclusion criteria. If the assessments are different, discrepancies will be resolved through consensus or referral to a third reviewer (AHV). All the registries included will go to the second phase for full-text evaluation by the same two authors (FAB-L and GWB-M). In case of disagreement, a third review author (AHV) will discuss and resolve the disagreements about the inclusion or exclusion of that article(s). If a study does not contain enough information to be included or excluded, we will contact the study investigators to obtain the necessary information and reassess the study after we receive the information. We will give the study investigators 2 weeks to respond, in the absence of response, the information will be reported as missing data, or the study will be excluded.

Data extraction

Two review authors (FAB-L and GWB-M) will independently extract data for the primary and secondary outcomes, using a table in the Microsoft Excel 365 worksheet developed by all authors, and resolve any disagreement through discussion. The following characteristics will be extracted for each study: Publication details (setting/year), Methodology, Type of participants, Type of intervention, Control, Outcomes, Duration and follow-up, Sample size, Age of each intervention group, Funding/conflict of interest. One author (FJVL) will check the accuracy of the data extracted.

Assessment of risk of bias of the studies included

Two reviewers will independently assess of the risk of bias in each randomised trial included using the Cochrane 'risk of bias' tool (RoB 2)[15] considering selection, performance, detection, attrition, reporting, and other biases, or the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for non-randomised studies.[16]

Statistical and analytical plans

The present study will be reported in accordance with the PRISMA statement for Systematic reviews and Meta-analyses.

The general data of the publications and the specific data related to the objective of this study will be collected in summary tables. If appropriate, in order to examine the effect of late revascularisation on clinical outcomes of interest, the risk ratio or odds ratio with a 95% confidence interval (CI) for dichotomous outcomes in each study will be extracted or calculated from the revascularisation with PCI versus non-revascularisation for the pooled analysis. Continuous outcomes will be summarised as mean differences. The level of heterogeneity of the studies included will be determined with the I^2 statistic and p value.[17] If I^2 is more than 50%, heterogeneity is considered substantial, and a meta-analysis will be performed using a DerSimonian and Laird random-effect model. The meta-analysis results will be displayed in a forest plot with 95% CIs. If appropriate, we will perform subgroup analyses based on the characteristics of the participants (according to country, region, age, and hours) or design of the studies included. Publication bias will be assessed using funnel plot asymmetry testing and Egger's regression test when ≥10 studies are included.

A two-tailed $p<0.05$ value will be used for statistical significance, and all meta-analyses will be performed using the package *meta* from R 4.0.3 (www.r-project.org).

If a meta-analysis is not possible, quantitative data will be presented in a narrative review using descriptive summaries and tables.

Sensitivity analysis

We will conduct a sensitivity analysis to assess the reliability of the meta-analysis by iteratively removing one study at a time to confirm that our findings were not driven by any single study. The *metainf* command integrated in the *meta* package of R 4.0.3 (www.r-project.org) will be used for the sensitivity analysis. Also, a sensitivity analysis using only studies with a low risk of bias will be performed.

Assessment of certainty of the evidence

We will assess the certainty of the evidence for each primary outcome according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance.[18] We will make a Summary of Findings (SoF) table for primary outcomes. We will classify the certainty of the evidence for each outcome as high, moderate, low or very low. We will initially rate the certainty for each outcome as high, as data come from RCT, and will be lowered in presence of important bias, indirectness or inconsistency in results, imprecision in estimates, or suspicion of publication bias. We will explicitly state if a specific outcome has not included studies. In this case, we will not assess the certainty of evidence. We will also report the main findings of the SoF table in plain language, according to their specific assessment of the certainty of evidence.

Ethics and dissemination

Due to the nature of this systematic review, which involves data collection without direct human participation in bibliographic databases, approval by an ethics committee will not be sought. The results of this systematic review will be published in peer-reviewed journals and presented at a congress or conference.

Patient and public involvement

No patient involved.

DISCUSSION

This review will allow assessing whether late revascularisation affects cardiovascular mortality, non-fatal myocardial infarction, hospitalisation for heart failure, and the appearance of unfavourable outcomes in patients with STEMI. The results will contribute to the knowledge of the benefits of late revascularisation in patients with STEMI in different contexts, especially in low-income and middle-income countries (LMIC), in which health systems have limited resources.

In LMIC, patients with STEMI often present late to health facilities and have longer ischaemic times.[19] This problem could be due to the lack of implementation of regional systems of care for patients with STEMI due to the lack of adequate financial, economic and human resources, which is an important deficiency that generates higher indicators of mortality and complications in these countries.[20 21] In addition, emergency medical services and catheterisation laboratories are poorly equipped and are more frequently found in urban areas. Therefore, patients living in rural areas have a higher risk of mortality from STEMI, due to poorly equipped transportation systems and the lack of a prehospital care system making access to health facilities difficult.[22] For this reason, the benefits of late revascularisation must

be appropriately addressed, especially in LMIC, in which patients with STEMI are a major challenge for healthcare systems.

Currently, the COVID-19 pandemic has led to a decrease in hospital admissions for acute coronary syndrome, resulting in an even greater reduction in the revascularisation rate in patients with STEMI.[23 24] This problem has been observed in LMIC such as Peru, in which approximately 50% of hospitalisations have been late and reperfusion therapy has been delayed, increasing the rate of acute complications due to STEMI during the pandemic.[25] Thus, the results of the present review would contribute to the current medical knowledge to establish an adequate approach for patients who present late to health facilities and to assess the indicators of mortality and complications due to this pathology.

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Contributors MC-D conceived the original idea for this systematic review. AH-V and RV-F drafted the manuscript. DC designed the search strategy. RV-F, MC-D, GWB-M, FAB-L, FJV-L and AH-V revised the search strategy. MC-D provided content expertise on myocardial reperfusion and ST-elevation myocardial infarction. All authors read, critically reviewed, provided feedback and approved the final manuscript. AH-V is the guarantor of the review. All authors agreed to publish this protocol and to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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