BMJ Open

Tirofiban efficacy and safety for percutaneous coronary intervention in patients with acute coronary syndrome: protocol for a systematic review and meta-analysis

Daniel Andries Gigliotti ,[1,2] Márcia Gisele Santos da Costa ,[1] Ana Helena Silva Santos ,[1,3] Marcelo G Correia ,[4,5] Marisa Santos [1]

To cite: Gigliotti DA, Santos da Costa MG, Santos AHS, *et al*. Tirofiban efficacy and safety for percutaneous coronary intervention in patients with acute coronary syndrome: protocol for a systematic review and meta-analysis. *BMJ Open* 2025;**15**:e093477. doi:10.1136/bmjopen-2024-093477

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-093477).

Received 07 September 2024
Accepted 25 April 2025

For numbered affiliations see end of article.

Correspondence to
Daniel Andries Gigliotti;
dagmachado1@gmail.com

ABSTRACT

Introduction Percutaneous coronary interventions (PCI) have become a cornerstone in the management of acute coronary syndromes (ACS), yet they carry risks of complications like stent thrombosis and reinfarction. Glycoprotein IIb/IIIa inhibitors, particularly tirofiban, have been employed as adjunctive therapies to reduce these risks. Despite its potential benefits, the use of tirofiban remains a subject of debate, with varying recommendations across major clinical guidelines.

Methods and analysis We systematically searched five databases from 1 January 1992 to 1 April 2025, including Medline, Embase, Lilacs, Clinicaltrials.org and Cochrane Central Register of Controlled Trials (CENTRAL), in addition to three grey literature databases. Randomised controlled trials and cluster randomised trials investigating the use of intravenous or intracoronary tirofiban in patients with ACS, unstable angina or myocardial infarction were considered for inclusion. Only published studies in English, Portuguese, Spanish and French were included. Data selection and extraction will be performed independently by two researchers, with any inconsistencies resolved with consensus or by consulting a third senior researcher. The risk of bias will be assessed through the risk of bias measurement tool (Rob-2) for interventions and/or cluster trials by two researchers independently, and the overall certainty of evidence will be assessed by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. A meta-analysis will be carried out if there is sufficient homogeneity between studies, with subgroup analysis being performed if significant heterogeneity is detected. Additionally, a metaregression model will be conducted if sufficient data are available.

Ethics and dissemination As this study involves secondary analysis of published data, ethics approval is not required. The results will be disseminated through peer-reviewed publication, conference presentations and will be shared with relevant clinical guideline committees.

PROSPERO registration number CRD42024585252.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will include research published up to 1 April2025, ensuring that the most recent and relevant evidence is considered for synthesis.
⇒ We will use rigorous methodology based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions, and results will be reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ The search strategy will encompass a large number of databases, ensuring a comprehensive overview of evidence.
⇒ While focusing on whether randomised controlled trials increases the reliability and robustness of data, it can exclude insights provided by observational studies.

INTRODUCTION

Acute coronary syndrome (ACS) is one of the major causes of morbimortality worldwide, accounting for ~40% of deaths from cardiovascular causes.[1] ACS consists of several clinical conditions caused by an abrupt imbalance between oxygen consumption and demand in myocardial cells. This imbalance typically results from, among other causes, the reduction of blood flow due to coronary obstruction.[2 3] The patient may present with dyspnoea, nausea and acute chest discomfort, often associated with pain radiating to the arms, jaw or neck.[3 4] According to the European Society of Cardiology, ACS refers to a range of conditions characterised by recent changes in clinical symptoms or signs, with or without abnormal findings on a 12-lead ECG or elevated cardiac troponin levels. It can include acute myocardial infarction or unstable angina.[5] The goal of the management strategies is to restore blood flow in the coronary arteries and prevent future ischaemic events and other complications. Therefore, reperfusion strategies, such as fibrinolysis and percutaneous coronary

intervention (PCI),[6] are widely used in association with pharmacological therapies, such as anticoagulants and antiplatelets.[7 8]

Tirofiban is one of the antiplatelets available and consists of a glycoprotein IIb/IIIa inhibitor that limits the interaction between fibrinogen and glycoprotein IIb/IIIa.[9] It can be administered intravenously before the exploratory angiographic procedure (upstream) or afterward (downstream).[10]

However, there is no consensus in the literature on the ideal therapeutic regimen of GP IIb/IIIa inhibitors. The European guideline on ACS gives a IIa recommendation (weight of opinion/evidence is in favour of its use) for the use of glycoprotein IIb/IIIa inhibitors in periprocedural complications with level C of evidence, while contraindicating pretreatment with a level of evidence A (derived from several randomised controlled trials [RCTs] and meta-analyses).[5] The American Heart Association, on the other hand, gives a class I recommendation (strong recommendation on its use) on glycoprotein IIb/IIIa use in high-risk patients undergoing PCI not adequately treated with $P2Y_{12}$ inhibitors and a class IIa recommendation for high-risk patients previously treated with antiplatelet therapy, with the level of evidence A and B (limited evidence), respectively.[11]

Several systematic reviews have assessed tirofiban efficacy in the past.[10 12] Given the significant burden of cardiovascular diseases and the potential role of glycoprotein IIb/IIIa inhibitors in managing patients undergoing PCI, it is essential to thoroughly evaluate the current evidence on the use of tirofiban. This systematic review aims to consolidate current evidence on the effectiveness of tirofiban therapy for patients with ACS undergoing PCI compared with control on preventing death at several time points and preventing reinfarction. The last systematic review on the topic was made in 2012,[12] and since then, new RCTs have been published that may help clarify the topic. By synthesising data from diverse studies, we seek to provide clearer guidance for clinicians and inform updates to existing clinical guidelines.

MATERIALS AND METHODS

This protocol for systematic review follows the principles recommended in Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).[13]

Eligibility criteria

The studies will be selected according to the following criteria:

Types of studies

In this review, we will be searching for RCTs or cluster-randomised trials investigating the use of intravenous or intracoronary tirofiban in the context of patients undergoing PCI.

Participants

Patients with ACS, unstable angina or myocardial infarction treated with intravenous or intracoronary tirofiban, either upstream or downstream, undergoing PCI in any care setting, for example, in hospital or ambulatory environments. There will be no age restriction on participants or on the follow-up time.

Outcome measures

The primary outcomes of the studies will be assessed using the risk ratio as the measure of association. Clinically, significant hard endpoints, including 1-year mortality and 30-day recurrence of myocardial infarction, will be evaluated among patients treated with tirofiban compared with control subjects following the procedure, as these are the outcomes associated with the drug's effectiveness.

Secondary outcomes to be assessed include the adverse events related to the intervention, including allergic reactions, thrombocytopenia and major or minor bleeding.

Exclusion criteria

Studies lacking follow-up after hospital discharge will be excluded.

Search methods for identification of studies

The research was conducted in the following databases: Medline, Embase, Lilacs, Clinicaltrials.org and Cochrane Central Register of Controlled Trials (CENTRAL) from 1992 to 1 April 2025. Only studies published in English, Portuguese, Spanish and French will be considered. In addition to database searches, a manual search will also be conducted by cross-quotations and searching the reference list of primary studies. Moreover, specialists on the topic will also be consulted to solicit pertinent references. Congress proceedings from societies or industry-backed conferences will also be searched for relevant literature. The PubMed draft of the search strategy is as follows:

(((AcuteCoronarySyndrome[MeSHTerms]) OR (Acute Coronary Syndrome[Title/Abstract])) OR (Acute Coronary Syndromes[Title/Abstract])) AND (((((((((tirofiban[MeSH Terms]) OR (tirofiban[Title/Abstract])) OR (Aggrastat[Title/Abstract])) OR (Agrastat[Title/Abstract])) OR (L-700,462[Title/Abstract])) OR (MK 383[Title/Abstract])) OR (MK-383[Title/Abstract])) OR (Tirofiban Hydrochloride[Title/Abstract])) OR (Tirofiban Hydrochloride Monohydrate[Title/Abstract]))

In addition to that, grey literature searches will also be done in the following databases: ProQuest Dissertations and Theses, WorldCat and Open Grey.

The protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO registration number CRD42024585252)

Data collection and analysis

Selection of studies

The title and abstract of the studies will be imported into Rayyan (https://www.rayyan.ai)[14] for text screening based on the predefined PICO criteria. Selection of studies will be conducted by two independent and blinded reviewers. Any inconsistencies will be resolved either by consensus or by consulting a third senior researcher. Authors from the primary studies may be contacted for missing outcomes

or inaccessible full texts. Studies without the full text and no responses from the researchers will be excluded from further assessment.

Data extraction and management

Two independent blinded researchers will perform data extraction including title, number of participants in total and randomised into each group, study population characteristics, age, type of intervention (downstream or upstream dosage and bolus dose), concomitant drugs in use, outcomes assessed, time of follow-up and funding. Any discrepancies will be resolved through consensus. Extracted data from valid studies will be compiled into a CSV table for further analysis and table construction.

Quality assessment

The risk of bias assessment in the studies will be assessed by two blinded researchers with the risk of bias measurement tool (Rob-2) for interventions and/or cluster trials, developed by Cochrane Collaboration.[15] This tool helps to do a systematic evaluation of the risk of bias in different domains, being in the randomisation process (for cluster trials, there is an additional domain, the risk of bias in the formation of a cluster), bias arising after the assignment to intervention, missing outcome data and in the measurement of the outcomes. Study bias may be categorised as being overall 'high', 'some concerns' or 'low', depending on the risk of bias of each domain.

After all body of evidence is presented, two independent blinded reviewers will each perform the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[16] system to assess the overall certainty of evidence for all outcomes presented. Any inconsistencies will be resolved through consensus or by consulting a senior researcher.

Data analysis and statistical considerations

The statistical analysis will be conducted using Review Manager software version 5.4 by Cochrane collaboration. The primary analysis will be done using data from the selected RCTs. For dichotomous outcomes (eg, mortality and reinfarction), the values will be expressed as risk ratio and the effect estimates will be calculated with 95% confidence intervals.

Meta-analysis will be done if there is sufficient homogeneity between studies in terms of intervention type, population, comparators and outcomes. It'll be presented in forest plots, offering a visual summary of the effect sizes across studies. The heterogeneity will be assessed using a χ^2-test and quantified using I^2. An I^2 value between 0% and 40% may indicate low heterogeneity, 30% and 60% as moderate, values exceeding 50% and 90% as substantial and 75% and 100% as considerable.[17] If significant heterogeneity is detected, a subgroup analysis will be conducted based on comorbidities or age groups present in the selected studies. A random-effects model will be used to account for potential variability between studies.

Additionally, the potential of publication bias will be analysed through the visual inspection of a funnel plot and, to complement the visual assessment, an Egger test will be applied to verify publication bias and heterogeneity.

If sufficient studies are available, meta-regression will be conducted to explore the impact of continuous variables (eg, age and dosage) on the outcomes.

Timeline

This systematic review will commence on 1 April 2025 and is projected to be completed by November 2025, allowing for a minimum duration of 9 months to ensure thoroughness and methodological rigour. The estimated duration for each phase of the review process is outlined as follows.

The finalisation of the protocol, including PROSPERO registration and confirmation of the eligibility criteria, will require approximately 1 week. The literature search, encompassing electronic databases and grey literature searches, will take an estimated 4 weeks. Screening of titles and abstracts by two independent reviewers will follow and is expected to take an additional 4 weeks.

The full-text review of potentially eligible studies and manual searches will be conducted over the course of 4 weeks. Data extraction, performed independently by two reviewers, will require approximately 3 weeks. This will be followed by a 4-week period for the risk of bias assessment using the Cochrane RoB-2 tool. The certainty of evidence for each outcome will then be assessed using the GRADE approach, over an estimated duration of 2 weeks.

Data synthesis and statistical analysis—including meta-analysis, heterogeneity assessment and publication bias evaluation—will be conducted over 5 weeks. Drafting of the systematic review manuscript will take an estimated 5 weeks, followed by 3 weeks for internal review and revision by all co-authors.

Finally, the review will undergo a period of formatting, final proofreading and submission preparation, which will require approximately 3–4 weeks.

Patient and public involvement

None

ETHICS AND DISSEMINATION

Since this study involves the secondary analysis of previously published data, ethical approval is not required. The findings will be disseminated through peer-reviewed publications and conference presentations and shared with relevant clinical guideline committees.

Author affiliations
[1]Núcleo de Avaliação de Tecnologias em Saúde, Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil
[2]Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

[3]Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[4]Biostatistics and Bioinformatics Department, National Institute of Cardiology, Rio de Janeiro, Brazil
[5]Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil

Contributors DAG is the guarantor. DAG, MS, AHSS and MGSdC all contributed to the conception of the study. The manuscript of the protocol was drafted by DAG, AHSS, MGSdC and MGC. MS revised the content. The search strategy was developed and run by DAG, AHSS and MGSdC. The selection and data extraction will be performed by AHSS and DAG, under the supervision of MGSdC. The risk of bias assessment will be conducted by MGSdC and DAG, supervised by MS. The statistical analysis and data synthesis will be carried out by MGSdC, DAG and MGC. The final review will be drafted by all the authors. The protocol was revised by all authors.

Funding This study was funded by the Brazilian Ministry of Health. The sponsors played no part in the design and writing of the protocol.

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.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Daniel Andries Gigliotti http://orcid.org/0009-0001-5008-181X
Márcia Gisele Santos da Costa http://orcid.org/0000-0003-3861-5257
Ana Helena Silva Santos http://orcid.org/0009-0008-7491-176X
Marcelo G Correia http://orcid.org/0000-0002-3446-5741
Marisa Santos http://orcid.org/0000-0002-2174-6800

REFERENCES

1 Timmis A, Vardas P, Townsend N, *et al*. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;43:716–99.
2 Sabatine MS, Cannon CP. Approach to the patient with chest pain. In: *Braunwald's heart disease: a textbook of cardiovascular medicine*. Elsevier, 2012: 1076–86.
3 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
4 Culić V, Eterović D, Mirić D, *et al*. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. *Am Heart J* 2002;144:1012–7.
5 Byrne RA, Rossello X, Coughlan JJ, *et al*. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720–826.
6 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet* 2003;361:13–20.
7 Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;39:213–60.
8 Eikelboom JW, Anand SS, Malmberg K, *et al*. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *The Lancet* 2000;355:1936–42.
9 Hashemzadeh M, Furukawa M, Goldsberry S, *et al*. Chemical structures and mode of action of intravenous glycoprotein IIb/IIIa receptor blockers: A review. *Exp Clin Cardiol* 2008;13:192–7.
10 Valgimigli M, Biondi-Zoccai G, Tebaldi M, *et al*. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J* 2010;31:35–49.
11 Amsterdam EA, Wenger NK, Brindis RG, *et al*. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. *J Am Coll Cardiol* 2014;64:e139–228.
12 Lang SH, Manning N, Armstrong N, *et al*. Treatment with tirofiban for acute coronary syndrome (ACS): a systematic review and network analysis. *Curr Med Res Opin* 2012;28:351–70.
13 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
14 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
15 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
16 Balshem H, Helfand M, Schünemann HJ, *et al*. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.
17 Deeks J, Higgins J, Altman D, *et al*. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, et al, eds. *Cochrane handbook for systematic reviews of interventions*. Cochrane, 2023.