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Percutaneous coronary intervention plus guideline-directed medical therapy (GDMT) versus GDMT alone in adults with stable coronary artery disease (Protocol).
Cochrane Database of Systematic Reviews 2026, Issue 1. Art. No.: CD016213.
DOI: 10.1002/14651858.CD016213.

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[Intervention Protocol]

Percutaneous coronary intervention plus guideline-directed medical therapy (GDMT) versus GDMT alone in adults with stable coronary artery disease

Arturo J Martí-Carvajal[1,2a], Mark J Dayer[3,4], Diana Monge Martín[2], Mario A Gemmato-Valecillos[5], Gabriella Comunián-Carrasco[1], Ricardo Riera Lizardo[1], Eduardo Alegría-Barrero[6], Ivan Perez-Neri[7], Irshad Bajeer[8], Bhone Myint Kyaw[9], Mona Abdalla[10], Raquel Esther Gonzalez Hormostay[11], Cristina Elena Martí-Amarista[12], Gursimer Jeet[13], José M Palacios-González[14], Fernando-María Caballero -Martínez[15]

[1]Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Valencia, Venezuela. [2]Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain. [3]Consultant Cardiologist, Mater Private Network, Dublin, Ireland. [4]Associate Professor, Royal College of Surgeons of Ireland, Dublin, Ireland. [5]Internal Medicine Program, NYC Health + Hospitals/Elmhurst | Icahn School of Medicine at Mount Sinai, New York, New York, United States. [6]Faculty of Medicine, Francisco de Vitoria University, Madrid, Spain. [7]Evidence Synthesis Unit, National Institute of Rehabilitation Luis Guillermo Ibarra Ibarra, Mexico City, Mexico. [8]Department of Pediatric Nephrology, Sindh Institute of Urology and Transplantation, SIUT, Karachi, Pakistan. [9]Centre for Population Health Sciences (CePHaS), Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. [10]Human Biology Department, School of Medicine, IMU University, Kuala Lumpur, Malaysia. [11]Asociación Cardiovascular Centro Occidental ASCARDIO, Barquisimeto, Venezuela. [12]Geriatric Medicine, JenCare Senior Medical Center, Berwyn, Illinois, USA. [13]Independent Consultant, Vancouver, Canada. [14]Ministerio de Salud Pública y Bienestar Social, Centro Médico Nacional, Departamento de Docencia e Investigación, Centro Médico Nacional, Departamento de Docencia e Investigación, Itaugua, Paraguay. [15]Unidad de Investigación, Área 6 de Atención Primaria, Madrid, Spain

[a]ORCID iD: https://orcid.org/0000-0001-8677-3351

Contact: Arturo J Martí-Carvajal, arturo.marti.carvajal@gmail.com.

Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 1, 2026.

Citation: Martí-Carvajal AJ, Dayer MJ, Monge Martín D, Gemmato-Valecillos MA, Comunián-Carrasco G, Riera Lizardo R, Alegría-Barrero E, Perez-Neri I, Bajeer I, Kyaw BM, Abdalla M, Gonzalez Hormostay REsther, Martí-Amarista CE, Jeet G, Palacios-González JM, Caballero -Martínez FM. Percutaneous coronary intervention plus guideline-directed medical therapy (GDMT) versus GDMT alone in adults with stable coronary artery disease (Protocol). *Cochrane Database of Systematic Reviews* 2026, Issue 1. Art. No.: CD016213. DOI: 10.1002/14651858.CD016213.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the clinical benefits and harms of percutaneous coronary intervention plus guideline-directed medical therapy compared with guideline-directed medical therapy alone for stable coronary artery disease in adults.

BACKGROUND

See Table 1 for acronyms and definitions.

Description of the condition

According to the 2019 European Society of Cardiology (ESC) Guidelines, stable coronary artery disease (CAD) is defined as a chronic condition with episodes of reversible myocardial ischaemia, typically induced by exertion or stress, but sometimes occurring spontaneously. It usually causes angina and is often associated with obstructive coronary artery disease, although it can also occur due to microvascular dysfunction. The condition is dynamic, potentially transitioning between stable and unstable phases over time (1). High-risk groups include older adults (> 75 years), people with diabetes, chronic kidney disease, multiple cardiovascular risk factors, prior myocardial infarction or revascularisation, and those with extensive ischaemia on testing (1).

Stable CAD silently affects millions worldwide, touching 1% to 4% of the global population (2). Its prevalence creeps upward with age, casting a long shadow over public health (3). This condition does not discriminate, but shows a preference for men and for women after menopause. Ischaemic heart disease is the leading cause of death worldwide (4). Beyond mortality, it leaves many grappling with disability and a diminished quality of life (5). The ripple effects extend to healthcare systems, straining resources with frequent doctor visits, an array of diagnostic tests, and complex procedures. While high-income countries bear a heavier burden, CAD is gaining ground in low- and middle-income countries, painting a picture of a truly global challenge. The economic toll is substantial, with treatment costs and lost productivity weighing heavily on societies (6).

Description of the intervention and how it might work

Percutaneous coronary intervention (PCI)

Percutaneous coronary intervention is a key therapeutic approach for adults with stable coronary artery disease (CAD), which aims to alleviate symptoms, improve quality of life, and reduce adverse cardiovascular events (5).

PCI encompasses several procedures tailored to address coronary artery stenoses, including the following.

- Balloon angioplasty: a catheter with a balloon that inflates at the site of blockage to restore blood flow. Drug-coated balloons (e.g. paclitaxel-coated) reduce restenosis risk (5, 7).
- Cutting balloon angioplasty: combines balloon inflation with small blades to score plaque, enhancing artery expansion (8)
- Atherectomy: removes plaque using devices, such as rotational (pulverises calcified plaque) (9, 10), directional (excises plaque) (9), or laser (vaporises plaque) (11)
- Stents:
  - Bare-metal stents: prevent artery recoil but have higher restenosis rates (12)
  - Drug-eluting stents: coated with medications (e.g. sirolimus) to inhibit cell proliferation, reducing restenosis (9, 13)
  - Bioabsorbable stents: designed to degrade over time, but have been associated with adverse events (14, 15, 16, 17)

These advancements aim to enhance procedural success, reduce complications, such as restenosis and stent thrombosis, and improve long-term outcomes in people undergoing PCI (18, 19, 20).

Guideline-directed medical therapy

Guideline-directed medical therapy enhances PCI outcomes and mitigates complications through (21, 22, 23):

- Antiplatelets: (e.g. aspirin, clopidogrel, ticagrelor) to prevent thrombosis (24);
- Lipid-lowering agents: (e.g. statins) to stabilise plaque (24);
- Blood pressure control: (e.g. angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers) (24);
- Angina relief: (e.g. nitrates, beta-blockers) (24).

Lifestyle modifications, such as a Mediterranean diet, physical activity, smoking cessation, and weight management are also essential for comprehensive CAD care (24).

Table 2 illustrates the categories of guideline-directed medical therapy for stable coronary artery disease and their corresponding therapies or lifestyle modifications. Guideline-directed medical therapy can also lead to adverse events, as outlined in Table 3.

The clinical benefits and harms of PCI may vary across different populations and clinical contexts. People with diabetes typically demonstrate reduced procedural success rates and accelerated restenosis, due to impaired vascular healing and more complex atherosclerotic disease patterns (25). People with chronic kidney disease face increased risks of contrast-induced nephropathy and poorer long-term outcomes following PCI (26). The extent and complexity of coronary disease also influences treatment effectiveness, with multivessel disease presenting greater technical challenges and different risk-benefit profiles compared to single-vessel involvement (27). Left ventricular function significantly impacts post-procedural outcomes, with people who have reduced ejection fraction showing different response patterns to revascularisation (28). Additionally, the presence of chronic total occlusions represents a distinct clinical scenario with unique procedural considerations and success rates (29). These population-specific differences justify the need for targeted subgroup analyses to better understand the differential effects of PCI across various population characteristics and clinical presentations.

Why it is important to do this review

Following guidance from Chapter 2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (30), we defined our research question as: what are the clinical benefits and harms of percutaneous coronary intervention plus guideline-directed medical therapy compared with guideline-directed medical therapy alone in adults with stable coronary artery disease?

Although this question has been extensively studied in randomised controlled trials, and synthesised in multiple meta-analyses (31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41), significant methodological limitations weaken the reliability and applicability of their findings. Common shortcomings include incomplete risk of bias assessments, heterogeneity in outcomes, such as myocardial infarction rates and anginal symptom relief, exclusion of older or

less contemporary studies, and insufficient sensitivity or subgroup analyses to explore population-specific outcomes. Additionally, under-reporting of adverse events and long-term outcomes leave critical gaps in understanding the full risk-benefit profile of PCI versus guideline-directed medical therapy. None of the previous analyses utilised GRADE to assess the certainty of the evidence or addressed statistical fraud. A recent systematic review has important limitations in the reporting and methodology of its trial sequential analysis (42).

This review seeks to overcome these limitations, providing a robust synthesis of the available evidence to guide clinical decision-making on the effectiveness and safety of PCI plus guideline-directed medical therapy in stable CAD.

OBJECTIVES

To evaluate the clinical benefits and harms of percutaneous coronary intervention plus guideline-directed medical therapy compared with guideline-directed medical therapy alone for stable coronary artery disease in adults.

METHODS

We will adhere to the *Cochrane Handbook for Systematic Reviews of Interventions* (43) and the *Methodological Expectations for Cochrane Intervention Reviews* (*MECIR*) for conducting the review (44), and the PRISMA 2020 guidelines for reporting (45).

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing percutaneous coronary intervention (PCI) plus guideline-directed medical therapy against guideline-directed medical therapy alone in adults (≥ 18 years) with stable coronary artery disease. The literature search will encompass studies conducted from 1977 onwards, marking the year when coronary angioplasty was first performed (46). We will consider evidence from both published and unpublished sources in any language.

We will exclude cross-over trials due to the nature of the intervention. Although we do not expect to identify cluster-randomised controlled trials, if identified, we will include and analyse them separately. We will include studies with any follow-up duration to capture both immediate and long-term outcomes, and we will conduct subgroup analyses based on follow-up periods, as needed.

We will exclude retracted trials.

Types of participants

We plan to include studies involving adults with stable coronary artery disease (CAD). For the purposes of this review:

1. Adults are defined as individuals aged 18 years and older;
2. Stable CAD is defined as:
   a. documented coronary artery stenosis ≥ 50% in at least one major epicardial vessel on coronary angiography or computed tomography angiography;
   b. presence of typical angina symptoms or evidence of ischaemia on non-invasive testing, including a positive stress test;
   c. absence of acute coronary syndrome within the past 30 days.

We will include studies conducted in outpatient and inpatient settings, with no restrictions on geographical location.

We will exclude studies focusing exclusively on participants with:

1. acute coronary syndromes;
2. prior coronary artery bypass grafting;
3. cardiogenic shock or haemodynamic instability;
4. prior incomplete revascularisation.

Rationale for population exclusions

We will focus on adults with stable coronary artery disease to evaluate the comparative effectiveness of PCI plus guideline-directed medical therapy versus guideline-directed medical therapy alone in a chronic disease setting, where the urgency for revascularisation is less pressing than in acute presentations, such as unstable angina, myocardial infarction, or cardiogenic shock. Excluding participants with prior coronary artery bypass grafting or incomplete revascularisation ensures a more homogeneous population, and aligns with our objective to assess outcomes specifically related to initial PCI plus guideline-directed medical therapy versus guideline-directed medical therapy alone in stable CAD.

Population groups

We will stratify our analyses based on the following population groups:

1. Risk based on extent/location of disease:
   a. Low risk: single-vessel disease, non-proximal left anterior descending artery
   b. Intermediate risk: two-vessel disease or proximal left anterior descending artery
   c. High risk: three-vessel disease or left main stem disease
2. Presence or absence of comorbidities:
   a. No diabetes, renal dysfunction, or peripheral arterial disease
   b. Diabetes only
   c. Renal dysfunction only (defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2)
   d. Peripheral arterial disease only
   e. Any combination of diabetes, renal dysfunction, and peripheral arterial disease
3. Left ventricular function (however assessed – echo/magnetic resonance imaging/other methods, e.g. multi-gated acquisition scan, quantification of angiography images), including reversibility/viability/hibernation:
   a. Normal (left ventricular ejection fraction ≥ 50%)
   b. Mid-range (left ventricular ejection fraction 41% to 49%)
   c. Reduced (left ventricular ejection fraction ≤ 40%)
   d. Severely reduced (left ventricular ejection fraction < 30%)
4. Length of follow-up:
   a. Short-term: studies with follow-up of less than one year
   b. Medium-term: studies with follow-up of one to five years
   c. Long-term: studies with follow-up of more than five years
5. Use of intracoronary imaging modalities (pre/post):
   a. Studies using intravascular ultrasound

   b. Studies using optical coherence tomography
   c. Studies that do not use advanced imaging modalities
6. Use of intracoronary physiology (pre/post):
   a. Fractional flow reserve
   b. Instantaneous wave-free ratio
   c. Other methodology: e.g. coronary flow reserve, quantitative flow ratio, resting full cycle ratio, hyperaemic stenosis resistance index, etc.
7. Use of different antiplatelet agents, including combinations and durations
8. Use of different stent types and methodologies for opening coronary arteries (8, 47)
9. Use of different methodologies for deploying multiple stents, e.g. shotgun, crush, culotte (48)

These population groups will allow us to evaluate the clinical benefits and harms of PCI plus guideline-directed medical therapy compared to guideline-directed medical therapy alone across specific subgroups. This stratification will help explore potential heterogeneity in treatment effects across different risk categories and participant characteristics in stable CAD, providing clinically relevant information for decision-making.

Types of interventions

We will include RCTs that compare percutaneous coronary intervention plus guideline-directed medical therapy with guideline-directed medical therapy alone in adults with stable coronary artery disease.

By definition, all eligible studies must explicitly report the use of PCI in the intervention arm; therefore, the search strategy is structured as CAD AND PCI. Identification of guideline-directed medical therapy occurs during the screening phase, as all included trials will specify guideline-directed medical therapy in their study design. This approach follows the methodological agreement with the Cochrane Information Specialist and is consistent with our focused comparison of PCI plus guideline-directed medical therapy versus guideline-directed medical therapy alone.

Intervention group

For the experimental group, we will include any percutaneous coronary intervention technique, encompassing balloon angioplasty, bare-metal stents, drug-eluting stents, and bioresorbable vascular scaffolds plus guideline-directed medical therapy. The PCI procedure will typically be performed in a cardiac catheterisation laboratory under local anaesthesia with conscious sedation. Access may be via femoral, radial, or brachial artery. Procedure duration may vary, but usually ranges from 30 minutes to 120 minutes. Post-procedure observation periods will be as specified in individual study protocols.

It is important to note that we will consider PCI-specific co-interventions, such as peri-procedural anticoagulation and antiplatelet therapy, to be part of the PCI strategy. This typically includes indefinite aspirin use and a P2Y12 inhibitor for a duration specified by the study protocol (minimum 1 month for bare-metal stents, 6 to 12 months for drug-eluting stents).

Control group

The control group will receive guideline-directed medical therapy according to recommendations from the American Heart Association/American College of Cardiology (AHA/ACC) guidelines (23), and the European Society of Cardiology (ESC) guidelines (1), which consist of comprehensive pharmacological treatment and lifestyle modifications. Guideline-directed medical therapy components generally include antiplatelet therapy (typically aspirin 75 mg to 100 mg daily, indefinitely), lipid-lowering therapy with statins, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers when indicated, glycaemic control for people with diabetes, and structured lifestyle modifications, such as smoking cessation programmes, exercise regimens, and dietary counselling. The delivery of guideline-directed medical therapy will be in an outpatient setting with regular follow-ups, and may involve a multidisciplinary approach, as specified in individual study protocols.

Intervention groupings with a description and eligible interventions

Intervention grouping	Description of intervention grouping	Eligibility criteria for interventions in the group

Percutaneous coronary intervention	Catheter-based procedures to improve blood flow to the heart muscle by opening narrowed coronary arteries	• Balloon angioplasty
		• Drug-eluting balloon angioplasty
		• Bare-metal stent implantation
		• Drug-eluting stent implantation
		  ○ Second-generation drug-eluting stents (e.g. everolimus-eluting, zotarolimus-eluting)
		  ○ Third-generation drug-eluting stents (e.g. biodegradable polymer stents)
		• Bioabsorbable stent implantation
		• Performed by trained interventional cardiologists
		• May involve single or multi-vessel procedures
		
		Must be combined with guideline-directed medical therapy, as defined in the comparator group.

Guideline-directed medical therapy	Comprehensive pharmacological treatment and lifestyle modifications to manage stable CAD	Guideline-directed medical therapy: • Antiplatelet therapy (e.g. aspirin, clopidogrel, ticlopidine, ticagrelor, prasugrel, cangrelor) • Lipid-lowering therapy (e.g. statins, ezetimibe, PCSK9 inhibitors) • Beta-blockers • Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers • For those with diabetes: consideration of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, or both • Lifestyle modifications (e.g. smoking cessation, exercise, dietary changes) • Managed, provider-led healthcare

Outcome measures

To choose the outcomes of this review, we followed the principles of the Core Outcome Measures in Effectiveness Trials (49). Table 4 shows the minimal clinically important differences for critical and important outcomes, based on the respective systematic reviews and meta-analyses.

Critical outcomes

1. **Overall survival:** defined as the percentage of individuals in a group who are alive after a fixed duration of time (50)
2. **Quality of life**. For our assessment of quality of life, we will adopt a flexible approach to accommodate the variety of validated scales used across different trials. We recognise that researchers may have employed various instruments (e.g. 51; 52; 53; 54). Our analysis will accept data from any validated quality of life scale used by the trialists. In cases where multiple trials have used the same validated tool, we will combine their scores. However, if different validated tools have been used across trials, we will either combine their scores, if they measure the same underlying concept, or select the quality of life tool used in the trials with the highest number of participants providing data for an outcome. We remain open to combining data from other validated tools used in the trials if they measure similar concepts. To ensure methodological rigour, we will consult the *Cochrane Handbook for Systematic Reviews of Interventions* for additional guidance on handling quality of life data (55).
3. **All-cause cardiovascular mortality**
4. **Serious adverse events**. We plan to collect specific adverse events, including serious bleeding, high-dose statin toxicity, and procedure-related complications (for the PCI group). Due to the lack of uniform terminology and standardisation when documenting adverse effects in research studies, which poses challenges for authors conducting reviews, we will follow the recommendations in Section 19.1.1 of the *Cochrane Handbook* [56]. We will accept any definition reported by the trial authors as major adverse events. We will separately assess peri-procedural myocardial infarction (MI), defined as MI occurring within 48 hours of the procedure. The diagnostic criteria for peri-procedural MI differ from those of spontaneous MI and are outlined in consensus documents, such as the Fourth Universal Definition of Myocardial Infarction (2018) (57). The biomarker-based diagnosis requires:
   a. elevation of cardiac biomarkers (troponin) > 5 times the upper reference limit in participants with normal baseline troponin levels;
   b. a further rise of at least 20% in participants with elevated baseline troponin;
   c. evidence of ischaemia (e.g. ECG changes, imaging abnormalities) to support the diagnosis.

To report the adverse events, we will follow the principles in Chapter 19 of the *Cochrane Handbook* (56).

Specific critical outcome measures for each outcome category

Broader outcome grouping	Outcome domain	Outcome measures
Mortality	Overall survival	Time-to-event analysis Kaplan-Meier method at 30 days, 1 year, and 5 years
Quality of life	Health-related quality of life	Short Form-36, Kansas City Cardiomyopathy Questionnaire, Seattle Angina Questionnaire, EuroQol 5-Dimension or any other validated quality of life scale used by trialists. Time of analysis: baseline, 6 months, 1 year, and 2 years.
Mortality	Cardiovascular mortality	Dichotomous (yes/no) Relative risk (95% confidence interval)

Serious Adverse events	Major bleeding	Incidence of major bleeding using standardised definitions at 30 days, 1 year, and 5 years (58)
	High-dose statins	Atorvastatin 40 mg to 80 mg Rosuvastatin 20 mg to 40 mg (59)
	Procedure-related complications	Incidence of procedure-related complications (for PCI group) at 30 days, 1 year, and 5 years (e.g. contrast-induced acute kidney injury, defined as an absolute serum creatinine increase of ≥ 0.5 mg/dL (44 µmol/L) or a ≥ 25% relative increase in absolute serum creatinine from baseline within 48 to 72 hours of iodinated contrast media exposure) (26). However, we will accept any definition reported in the included trials.

Important outcomes

1. **Symptom relief (angina)**
   a. Measurement: Canadian Cardiovascular Society Angina Classification (60).
2. **Total myocardial infarction** (fatal and non-fatal)
   a. Measurement: incidence of myocardial infarction (using standardised definition)
3. **Repeat revascularisation**
   a. Measurement: incidence of repeat percutaneous coronary intervention
4. **Left ventricular function**
   a. Measurement: ejection fraction by echocardiography or cardiac MRI or any other methods reported by trial authors

The cross-over ratio, defined as the proportion of participants initially allocated to guideline-directed medical therapy who later switch to PCI, provides a valuable dimension in outcome analysis. Our goal is to demonstrate that including the cross-over ratio does not increase the number of outcomes, but rather deepens our understanding of each outcome's implications. We plan to analyse all outcomes with the cross-over ratio as a key factor, allowing for a more accurate and meaningful interpretation of results. Incorporating cross-over data enhances reliability by mitigating bias, reducing the risk of misinterpreting each treatment's true efficacy. The cross-over ratio also allows for a more comprehensive analysis by capturing real-world treatment dynamics, moving beyond a simplistic binary comparison. Furthermore, it improves clinical and policy relevance by clarifying which treatment approach may be better suited for specific groups. In summary, evaluating all outcomes with the cross-over ratio result enables a nuanced and realistic analysis, enriching the practical value of systematic reviews comparing PCI and guideline-directed medical therapy (61). Specifically, the cross-over ratio allows us to assess treatment efficacy, durability, patient satisfaction, and external validity—offering a deeper understanding of these perspectives without adding additional outcomes, but instead, expanding the depth of insights gained (57).

Specific important outcomes measures for each outcome category

Broader outcome grouping	Outcome domain	Outcome measures
Clinical symptoms	Angina	Canadian Cardiovascular Society Angina Classification (60). Time points: baseline, 6 months, 1 year, 2 years, other methods reported by trial authors
Adverse cardiac events	Total myocardial infarction	Incidence of myocardial infarction (any standardised definition) Time points: 1 year, 5 years
Adverse cardiac events	Repeat revascularisation	Incidence of repeat percutaneous coronary intervention Time points: 1 year, 5 years
Cardiac function	Left ventricular function	Ejection fraction measured Echocardiography Cardiac magnetic resonance imaging Other methods reported by trial authors Time points: baseline, 1 year
Treatment efficacy	Cross-over ratio	Percentage of participants crossing over from guideline-directed medical therapy to PCI

Treatment durability	Cross-over influence on clinical events	Re-assessment of primary outcomes (e.g. mortality, MI) with cross-over adjustment
Patient satisfaction	Cross-over ratio	Rate of cross-over due to patient-reported insufficient symptom relief
External validity	Cross-over impact on generalisability	Analysis of how cross-over affects generalisability of PCI and guideline-directed medical therapy findings

We will not conduct any economic analysis in this Cochrane review.

Search methods for identification of studies

To minimise bias in our search results, we will follow the guidance in Chapter III and Chapter 4 of the *Cochrane Handbook* (62, 63, 64), and in PRISMA-S (65), to plan and describe the search process for the review.

Electronic searches

We will follow PRISMA 2020 guidance #6 by specifying all databases, registers, websites, and other sources that will be searched or consulted to identify studies. We will also specify the date when each source is last searched or consulted (45).

The search will encompass studies conducted from 1977 onwards, marking the year when coronary angioplasty was first performed.

After consultation with the Cochrane Information Specialist, we will apply an RCT filter to manage search yield. As a result, the main electronic search strategy will not retrieve observational studies, and observational evidence for adverse events will not be identified through these searches.

For each bibliographic database, we will adopt the following scheme:

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library (1977 to search date);
2. MEDLINE (1977 to search date);
3. Embase Ovid (Excerpta Medica Database; 1977 to search date);
4. LILACS (Latin American and Caribbean Health Science Information database; BIREME; 1977 to search date);
5. Conference Proceedings Citation Index – Science (Web of Science; 1977 to search date).

We will not restrict the language of publication or publication status.

We will not perform a separate search for adverse effects of interventions. We will consider adverse effects described in the included studies only.

We will search for suspected predatory journals, defined as entities that misrepresent themselves as scholarly journals for financial gain while failing to meet academic publishing standards (66). Their practices include aggressive solicitation of manuscript submissions, promises of rapid publication times, lack of transparency regarding article processing fees, and the absence of essential editorial processes, such as peer review, archiving, and conflict of interest management. They often mimic reputable journals through similar names and branding, fabricate citation metrics, and list individuals on editorial boards without consent (66). We will search in the Predatory Journals list.

The preliminary search strategies for MEDLINE, with the expected date range of the searches, are shown in Supplementary material 1. We will provide the actual date of the electronic searches at the review stage.

Searching other resources

We will search the US Food and Drug Administration (FDA; www.fda.gov), European Medicines Agency (EMA; www.ema.europa.eu/ema/), World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/), and ISRCTN registry (www.isrctn.com/) for ongoing trials.

Data collection and analysis

To ensure methodological integrity and minimise conflicts of interest, review authors will not participate in study selection, data extraction, risk of bias assessment, or GRADE evaluation for any trials in which they were directly involved as principal investigators, co-investigators, or co-authors.

To minimise bias in our search results, we will follow guidance from Chapter 4 of the *Cochrane Handbook* (64). We will also refer to Chapter III of the *Cochrane Handbook* to ensure adherence to Cochrane's conduct standards for selecting studies and methodological best practices (63). For the appropriate collection of data, we will follow the guidance outlined in Chapter 5 of the *Cochrane Handbook* (67).

Selection of studies

We will follow the recommendations in Chapter 4 of the *Cochrane Handbook* (64). We will use Covidence to manage the results of our search (68).

Four review authors (JMPG, FCM, Cristina Martí-Amarista (CMA), and Raquel González (RG)) will independently and in duplicate screen titles and abstracts of the reports identified by the search. We will code the reports as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, other authors will be asked to arbitrate (AMC, Mark Dayer (MD) and Eduardo Alegría (EA)).

José M Palacios González (JMPG) and Fernando Caballero Martínez (FCM) will manually check citations and reference lists of the included studies and any relevant systematic reviews identified. We will also search for relevant grey literature sources, such as reports, dissertations, theses, and conference abstracts, e.g. in

Google Scholar (scholar.google.com/). Arturo Martí-Carvajal (AMC) will check any disagreements.

We will use the PubMed/MEDLINE 'similar articles search' tool on all included studies. We will manually check citations and reference lists of the included studies and any relevant systematic reviews identified.

We will also search for and examine any relevant retraction statements and errata for information, as errata can reveal important limitations or fatal flaws in included studies (64). We will check whether any of the identified studies have been retracted in the Retraction Watch Database 2021. We will list any trials that were retracted in the Excluded studies section.

We will use PRISMA-S items relevant to our review to ensure that we have reported and documented our searches as advised (45; 65).

We will retrieve the full-text publication of reports coded 'retrieve', and three review authors (Ricardo Riera (RR), Diana Monge Martín (DMM) and Mario Gemmato Valecillos (MGV)) will independently screen the full text, identify the trials for inclusion, and identify and record reasons for exclusion of the ineligible studies/reports. We will resolve any disagreement through discussion, or if required, we will consult the same arbitrators (AMC, MD, and EA). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table (45).

If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that report adverse events associated with percutaneous coronary intervention, we will review these studies for reports of adverse events. We will not specifically search for observational studies to include in this review, which is a limitation. We will acknowledge the limitations of this approach in the Discussion section.

Data extraction and management

We will employ a spreadsheet template to collect data on trial characteristics, initially piloted on a minimum of six trials included in the review. One author (AMC) will extract these data using artificial intelligence, specifically ChatGPT 5.2 (Presentamos ChatGPT | OpenAI), while three review authors (Gabriella Comunián-Carrasco (GCC), Bhone Myint Kyaw (BMK) and RQ) will manually verify all extracted information. Two authors (GC and AMC) will build a spreadsheet to include the characteristics of the included trials. Mark Dayer (MD), Eduardo Alegría (EA) and Iván Pérez-Neri (IPN) will check that section.

If we include 20 or more trials, more authors will contribute to data extraction to make the workload feasible. Any disagreements will be resolved through arbitration by either MD, EA, or IPN. Clarification required for accurate data extraction will be sought directly from the original trial authors. Extracted data will include trial methods (duration, cross-over rates, trial type), participant characteristics (age, sex, biomarkers, comorbidities), interventions (PCI details, stents, procedural imaging), outcomes, and funding/conflicts of interest. For summarising study characteristics and preparing for synthesis, we will adhere to Chapter 9 of the *Cochrane Handbook* (69). See Supplementary material 2.

We will note in the characteristics of included studies table if outcome data were not reported in a usable way, and when we transformed or estimated data from a graph. One review author (AMC) will transfer data into the RevMan file [70]. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports (IPN, IB, and Mona Abdalla (MA)).

We will apply the following decision rules in the event of multiple outcome reporting:

1. If both final values and change from baseline values are reported for the same outcome, we will extract final values.
2. If both unadjusted and adjusted values for the same outcome (for each treatment group) are reported, we will extract adjusted values.
3. If data are analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we will extract ITT data.
4. If multiple time points are reported, we will extract the closest time points reported in each trial up to our primary end points (30 days, 1 year, 5 years).
5. We will use WebPlotDigitizer to extract data from graphs or figures if means and measures of variance are not reported in the text of included studies [71].

Risk of bias assessment in included studies

We will follow the guidance in the Cochrane MECIR conduct standards, *Planning the review methods at protocol stage* and *Assessing risk of bias in included studies* (44).

Three review authors (AMC, IPN, and Irshad Bajeer (IB)) will independently and in duplicate assess the risk of bias for each study, using version 2 of the Cochrane risk of bias tool (RoB 2), outlined in the *Cochrane Handbook* (72, 73, 74). We will resolve any disagreements by discussion or by involving another author (MA). We will assess the risk of bias for all our review outcomes.

As we are interested in quantifying the effect of assignment to the interventions at baseline, we will use the intention-to-treat principle regardless of whether the interventions are received as intended.

We will use the following domains to assess the risk of bias in the individually randomised trials (Supplementary material 3):

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions (effect of intervention assignment)
3. Bias due to missing outcome data
4. Bias in measurement of the outcome. We will focus particularly on trials published after 2005 to verify their registrations and thus ensure the transparency and quality of the information used (75, 76).
5. Bias in the selection of the reported result

We will use the signalling questions in the RoB 2 tool to rate each domain as low risk of bias, some concerns, or high risk of bias (73, 74). The response options for the signalling questions will be:

1. yes;

2. probably yes;
3. probably no;
4. no;
5. no information.

We will use the most recent RoB 2 Excel tool (74). An algorithm, in Excel, maps the responses to the signalling questions per outcome, and proposes a risk of bias judgement for each domain.

When we judge a result to be at a particular level of risk of bias for an individual domain, it implies that the overall result has a risk of bias that is at least this severe. Therefore, a judgement of high risk of bias within any domain will have a similar implication for the trial results as a whole, irrespective of which domain is being assessed. Some concerns in multiple domains may lead the review authors to decide on an overall judgement of a high risk of bias for that outcome or group of outcomes (73).

We will use the overall risk of bias for a study result, rather than specific domains. The overall risk of bias for the result is the least favourable assessment across the domains of bias.

Overall risk of bias:

1. Low risk of bias will denote that the study will be judged to be at low risk of bias for all domains for this result.
2. Some concerns will denote that the study will be judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
3. A high risk of bias will denote that study will be judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

We will make this information available online (we will provide details at the review stage).

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

For time-to-event data (overall survival), we will estimate the hazard ratio (HR) with 95% confidence interval (CI).

For dichotomous data (adverse events (major and non-major), symptom relief (angina), myocardial infarction, repeat revascularisation, and categorised left ventricular function outcomes (e.g. preserved versus reduced ejection fraction using validated thresholds, left ventricular ejection fraction ≥ 50% versus < 50%)), we will calculate the risk ratio (RR) with 95% CI. For data presented as counts, we will utilise the rate ratio with 95% CI.

For continuous data (quality of life, symptom relief (angina), left ventricular function parameters—including left ventricular ejection fraction percentages, global longitudinal strain values, end-diastolic volumes, end-systolic volumes, and other quantitative echocardiographic indices), we will estimate mean differences (MD) with 95% CIs. When different scales are used for measuring quality of life or different imaging modalities are employed for assessing left ventricular function (e.g. cardiac magnetic resonance imaging versus echocardiography), we will use the standardised mean difference (SMD) with 95% CIs.

Following the guidance in Chapter 15 of the *Cochrane Handbook*, we will use the following minimal clinically important differences for interpreting our results [77]. However, we acknowledge the inherent uncertainty and variability in determining precise thresholds for minimal clinically important differences, as these may depend on the context, population, and outcome measure used.

We will assume minimal clinically important differences of:

1. 5 points on a 100-point scale for physical functioning, general health, and mental health (SF-36/RAND-36) (78);
2. 6.25 points for role − physical, and vitality (SF-36/RAND-36) (78);
3. 8 points for physical limitation (SAQ/SAQ-7) (78);
4. 10 points for bodily pain (SF-36/RAND-36) (78);
5. 16 points for quality of life (SAQ/SAQ-7) (78);
6. 25 points for angina stability (SAQ/SAQ-7) (78).

Table 4 provides a complete overview of the minimal clinically important differences for all critical and important outcomes, based on existing systematic reviews and meta-analyses.

As recommended in Section 6.5.1.2 of the *Cochrane Handbook* (79), where necessary, we will multiply the mean values from one set of studies by -1 to ensure that all the scales point in the same direction.

When necessary, we will estimate the mean and standard deviation from medians and interquartile ranges (80). When statistical information is missing in trial reports (such as standard deviations), we will attempt to extract the missing values from P values and 95% CIs.

We will calculate the number needed to treat for an additional beneficial outcome and the number needed to treat for an additional harmful outcome only for critical outcomes, as these measures provide the most relevant assessment of the clinical usefulness of treatment consequences for decision-making.

Where data are not reported in a usable format, we will attempt to convert them to the required format, following guidance in Chapter 6 of the *Cochrane Handbook* (79).

Unit of analysis issues

The unit of analysis in this Cochrane review will be the individual participant. For trials reporting multiple intervention groups, we will include only the groups relevant to our PCI plus guideline-directed medical therapy versus guideline-directed medical therapy alone comparison. To avoid double-counting when a single control group is used for multiple comparisons, we will split the control group evenly between comparisons, adjusting the sample size accordingly, while maintaining the same event rates.

For our critical outcome of adverse events, we will carefully distinguish between:

1. the frequency of participants experiencing at least one adverse event (e.g. three participants reporting any adverse event

such as bleeding, contrast-induced nephropathy, or access site complications); and
2. the total number of adverse events, accounting for multiple events in the same participant (e.g. one participant experiencing both an access site complication and contrast-induced nephropathy).

We will identify and note any instances where trials have inappropriately treated multiple events within the same participant as independent observations. When the reported number of events equals the number of participants, we will treat events as the unit of analysis, following the guidance in Chapter 6 of the *Cochrane Handbook* (79).

Since stable CAD is a chronic condition, and both PCI and GDMT are long-term management strategies, we do not anticipate including cross-over or cluster-randomised trials in this review.

Dealing with missing data

We will assess the number of dropouts for each included trial and for each intervention group and evaluate whether an intention-to-treat (ITT) analysis was conducted or could potentially be performed, based on the published information. To resolve uncertainties, we will contact the trial authors for additional data, if possible.

For an ITT analysis, we will request data from the trial authors regarding the number of participants in each treatment group, regardless of compliance, subsequent ineligibility, exclusion from treatment, or loss to follow-up. If an ITT analysis is not feasible, we will use the data available to us and perform an available case analysis as an alternative.

We will include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios (81):

1. **Best-worst case scenario analyses**: participants with missing outcome data are considered successes in the experimental group and failures in the control group. The denominator will include all the participants in the trial.
2. **Worst-best case scenario analyses**: participants with missing outcome data are considered failures in the experimental group and successes in the control group. The denominator will include all the participants in the trial.

Reporting bias assessment

For outcomes with 10 or more RCTs, we will generate funnel plots in RevMan to visually assess potential publication bias (82, 83). To strengthen our assessment of small-study effects and improve detection of asymmetry, we will also apply Harbord's and Peter's tests (84), using Stata statistical software (85). This combined approach aligns with *Cochrane Handbook* guidance (86), which recommends supplementing visual inspection with formal statistical tests when assessing reporting bias in meta-analyses of binary outcomes. We acknowledge that funnel plot asymmetry may indicate small-study effects rather than publication bias alone.

We will compare outcome data across trial publications, contact trial authors for missing information, and review trial registers and protocols.

Synthesis methods

We will adopt a random-effects meta-analysis model for our primary analyses, recognising that treatment effects may vary depending on the degree of synergy with supplementary interventions. This approach will allow us to estimate the average intervention effect, accompanied by 95% confidence intervals. To assess the robustness of our findings, we will conduct sensitivity analyses using a fixed-effect model (87).

We will determine the 95% prediction interval, which considers the whole distribution of the effects (88, 89). Prediction intervals in meta-analysis show the expected range of true effects in similar studies (90, 91). We will present 95% prediction intervals in RevMan when the random-effects model is applied, as recommended in Chapter 10.10.4.3 of the *Cochrane Handbook* (87). If there are 10 or more included trials and there is no asymmetry in the funnel plot for a particular outcome, we will estimate the 95% prediction interval (87).

We will conduct a meta-analysis with RevMan (70).

We will follow the recommendations provided for synthesising and presenting findings using alternative methods (92).

Investigation of heterogeneity and subgroup analysis

Assessment of heterogeneity and investigation of effect modifiers

We will systematically investigate heterogeneity and potential effect modification through several complementary approaches.

Statistical heterogeneity assessment:

1. Visual inspection of forest plots
2. Chi^2 test (considering $P < 0.10$ as indicative of significant heterogeneity)
3. I^2 statistic with a prespecified threshold (93): we will consider substantial statistical heterogeneity present when I^2 exceeds 75%. When substantial heterogeneity is identified ($I^2 > 75\%$), we will explore potential sources through meta-regression (if applicable) and subgroup analyses.

Meta-regression: for outcomes with 10 or more trials, we will conduct meta-regression using Stata software (85), to explore potential effect modifiers quantitatively.

1. Random-effects models with restricted maximum likelihood estimation (94)
2. Clinical covariates:
   a. Proportion of diabetic participants
   b. Baseline renal function (mean estimated glomerular filtration rate)
   c. Proportion of participants with multivessel disease
   d. Proportion of participants with chronic total occlusions
   e. Reduced ejection fraction versus preserved ejection fraction
3. Methodological covariates:
   a. Year of study publication
   b. Sample size (300 participants by comparison groups)

Results will be presented as regression coefficients with 95% confidence intervals.

The adjusted R^2 statistic will quantify the variance explained by covariates.

Subgroup analysis

All eligible studies will contribute to a single main synthesis. The population subgroups described below (e.g. diabetic versus non-diabetic participants) will not be analysed as separate PICO questions or distinct syntheses. Rather, we will explore potential differences in treatment effect across these subgroups using subgroup analyses and formal tests for interaction. This approach aligns with the recommendations in Chapter 3 and Chapter 10 of the *Cochrane Handbook*, where predefined subgroup analyses serve to explore heterogeneity and effect modification within a unified synthesis framework (95, 87).

We have identified five prespecified subgroup analyses based on clinical characteristics that may modify treatment effects:

1. Diabetic status (diabetic versus non-diabetic participants). Rationale: diabetes mellitus significantly impacts cardiovascular outcomes; people with diabetes have twice the mortality risk from coronary artery disease compared to non-diabetics. We hypothesise that diabetic status may modify the intervention effect, with potentially reduced effectiveness in diabetic participants due to more complex disease patterns and impaired vascular healing (25).
2. Renal function (chronic kidney disease versus non-chronic kidney disease). Rationale: chronic kidney disease (CKD) is associated with poorer outcomes following percutaneous coronary intervention. We anticipate that participants with CKD may demonstrate reduced benefit from the intervention due to higher procedural complications and accelerated disease progression (26).
3. Disease extent (multivessel versus single-vessel disease). Rationale: the complexity and extent of coronary artery disease may influence treatment effectiveness. We expect that participants with multivessel disease may show different treatment effects compared to those with single-vessel disease due to varying technical challenges and risk profiles (27).
4. Presence of chronic total occlusions (present versus absent) (29). Rationale: chronic total occlusions represent a distinct anatomical and technical challenge. We hypothesise that the presence of such lesions may modify treatment effects due to their complexity and associated procedural considerations.
5. Heart failure status (heart failure with reduced ejection fraction versus preserved ejection fraction versus no heart failure). Rationale: heart failure significantly impacts outcomes following coronary revascularisation; those with heart failure demonstrate distinct risk-benefit profiles and clinical outcomes after PCI compared to those without heart failure. This effect varies by ejection fraction status, potentially modifying treatment effectiveness and procedural outcomes. We hypothesise that participants with heart failure, particularly those with reduced ejection fraction, may show different treatment effects due to their complex cardiovascular pathophysiology and higher risk profile (28).

Methods for subgroup analyses

We will conduct analyses using study-level variables when studies can be clearly categorised into single subgroups. For studies reporting separate outcomes for different participant subgroups, we will use within-study contrasts to maximise available data. We will assess subgroup differences using the formal test for interaction in RevMan, with $P < 0.05$ indicating potential subgroup effects. We will interpret subgroup analyses cautiously, considering them hypothesis-generating rather than definitive.

If insufficient studies are available (less than 10 trials) or inadequate information is available to conduct meaningful subgroup analyses, we will report this as a protocol deviation in the Methods section, and discuss it as a limitation.

Additional heterogeneity investigation

We will explore clinical and methodological diversity through structured narrative synthesis, including:

1. Tabulation of key study characteristics;
2. Assessment of variation in intervention effects across different study designs and contexts;
3. Investigation of methodological factors, such as risk of bias and outcome measurement approaches.

This approach aligns with both PRISMA 2020 guidance (45) and the *Cochrane Handbook* (87), ensuring a systematic and transparent investigation of effect modification and heterogeneity (87, 44).

Equity-related assessment

We do not plan to conduct specific equity-related analyses in this review. However, we do plan to collect contextual factors and participant characteristics that could influence the results, such as ethnicity, culture, place of residence (urban or rural settings, low-, middle-, or high-income countries), sex, and socio-economic status. These factors will be summarised in a table outlining the participant composition in the included trials to aid in assessing the applicability of the results across different settings. We will adhere to the principles outlined in Chapter 16 of the *Cochrane Handbook* (96).

Sensitivity analysis

We plan to conduct the following sensitivity analyses:

1. Risk of bias assessment: comparing trials at low risk of bias with trials with some concern plus those with high risk of bias, addressing potential overestimation of beneficial effects and underestimation of harmful effects
2. Fixed-effect model meta-analysis: comparing results with the primary random-effects model and examining changes in effect estimates, confidence intervals, and heterogeneity
3. Complete case analysis of trials without missing data for all outcomes: comparing effect estimates, precision, and heterogeneity with the primary analysis
4. Comparison of trials without for-profit funding versus trials with for-profit funding: addressing potential funding bias affecting intervention benefits and harms (97)
5. Comparison of trials with high cross-over rates (≥ 10%) versus low cross-over rates (< 10%): evaluating the impact of cross-over on effect estimates, precision, and heterogeneity

For each sensitivity analysis, we will:

1. present forest plots for visual comparison;
2. document effect estimate differences;

3. compare confidence intervals and heterogeneity measures;
4. provide narrative assessment of result robustness.

We will make informal comparisons, focusing on the magnitude and precision of effect estimates under different analytical assumptions, rather than relying on P value comparisons.

Certainty of the evidence assessment

We will create a summary of findings table with the following Critical outcomes (overall survival, quality of life, all-cause cardiovascular mortality, serious adverse events (major bleeding, high-dose statin toxicity, and procedure-related complications (for PCI group)) and Important outcomes (symptom relief (angina − number of people with improvement), myocardial infarction, repeat revascularisation). For each outcome, we will provide the primary time point for measuring the outcome (i.e. follow-up time, with mean/median and range).

For each outcome included in the summary of findings table, we will specify and report the primary time point of measurement (e.g. 30 days, 1 year, or 5 years), depending on the time point most commonly reported across the included studies. The assessment of risk of bias using RoB 2 will focus on the same time point selected for the summary of findings table to ensure alignment with the GRADE evaluation.

Three review authors (Ivan Pérez-Neri (IPN), Irshad Bajeer (IB), and GJ), working independently, will make judgements about the certainty of the evidence. We will resolve disagreements by discussion, or we will involve two authors (AMC and Mark Dayer (MD)). We will justify, document, and incorporate all judgements into the reporting of results for each outcome [77].

We will use the five GRADE factors (risk of bias, heterogeneity (consistency of effect), imprecision (calculating also the optimal information size), indirectness, and publication bias) to assess the certainty of the body of evidence as it relates to the trials that contribute data to the meta-analyses for the prespecified outcomes (98).

We will determine the control group risk through one of two methods. We will use the median risk when we derive our data from a meta-analysis. If we lack meta-analytic data, we will calculate the risk directly from the control group proportion.

We will use the methods and recommendations described in Chapters 13, 14, and 15 of the *Cochrane Handbook* (86, 98, 77) and PRISMA 2020 (45). We will use GRADEpro GDT (99). As listed in Types of interventions, we will only compare percutaneous coronary intervention plus guideline-directed medical therapy (experimental intervention) with guideline-directed medical therapy alone.

We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

We will communicate the findings of interventions following the GRADE Working Group's recommendations (100).

Consumer involvement

We will not involve consumers in this review due to limited resources.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016213.

Supplementary material 1 Search strategies

Supplementary material 2 Data extraction and management

Supplementary material 3 Risk of bias assessment

ADDITIONAL INFORMATION

Acknowledgements

We would like to express our heartfelt gratitude to Jordi Pardo Pardo for his invaluable recommendations regarding the protocol, particularly in the Equity section, the library staff of the Faculty of Medicine at the Universidad Francisco de Vitoria in Madrid, Spain, and Charlene Bridges, Information Specialist, Publishing and Technology Directorate, Cochrane Central Executive Team.

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Dr William Cayley Jr, Clinical Adjunct Professor, University of Wisconsin School of Medicine and Public Health, Eau Claire Medical Clinic, Eau Claire, WI
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Jenny Bellorini, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Jen Hilgart and Nuala Livingstone, Cochrane Central Editorial Service (methods); Jo Platt, Cochrane Central Editorial Service (search)

Contributions of authors

Conceptualisation: AMC, MD

Methodology: AMC, MD, DMM, MAGV, GCC, RRL, EAB, IPN, IB, BMK, MA, RGH, CEMA, GGJ, JMPG, FCM

Project administration: AMC

Supervision: AMC

Writing – original draft: AMC

Writing – review and editing: AMC, MD, DMM, MAGV, GCC, RRL, EAB, IPN, IB, BMK, MA, RGH, CEMA, GGJ, JMPG, FCM

Declarations of interest

- Arturo J Martí-Carvajal: none declared
- Mark Dayer: Abbott Vascular: grant to support a PhD student and MD student; Bevan Brittan: expert witness for cardiology cases, principally endocarditis and device-related matters
- Diana Monge Martín: none declared
- Mario A Gemmato-Valecillos: none declared
- Gabriella Comunián-Carrasco: none declared
- Ricardo Riera Lizardo: none declared
- Eduardo Alegría-Barrero: none declared
- Ivan Perez-Neri: none declared
- Irshad Bajeer: none declared
- Bhone Myint Kyaw: none declared
- Mona Abdalla: none declared
- Raquel Gonzalez Hormostay: none declared
- Cristina Elena Martí-Amarista: none declared
- Gursimerjeet GJ: none declared
- José M. Palacios-González: none declared
- Fernando Caballero Martínez: none declared

Sources of support

Internal sources

- Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain, Spain

  Institutional support and research infrastructure
- Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Valencia, Venezuela, Venezuela

  Institutional support and research infrastructure

External sources

- Cochrane Collaboration, UK

  Methodological training and editorial support

Registration and protocol

Cochrane approved the proposal for this review in January 2025.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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ADDITIONAL TABLES

Table 1. Overview of the glossary of acronyms and definitions

Acronym and term	Definition	Source
Angiotensin-converting enzyme inhibitors	A class of drugs whose main indications are the treatment of hypertension and heart failure. They exert their haemodynamic effect mainly by inhibiting the renin-angiotensin system. They also modulate sympathetic nervous system activity and increase prostaglandin synthesis. They cause mainly vasodilation and mild natriuresis without affecting heart rate and contractility. Year introduced: 1988	ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors) - MeSH - NCBI
Angiotensin II receptor blockers	Agents that antagonise angiotensin II type 1 receptor. Included are angiotensin II analogues, such as saralasin and biphenylimidazoles, such as losartan. Some are used as antihypertensive agents.	Angiotensin II Receptor Blockers - MeSH - NCBI

Table 1. Overview of the glossary of acronyms and definitions *(Continued)*

	Year introduced: 2005	
Coronary artery disease	Pathological processes of coronary arteries that may derive from a congenital abnormality, atherosclerotic, or non-atherosclerotic cause. Year introduced: 2008 (1987)	Coronary Artery Disease - MeSH - NCBI
Chronic kidney disease	Conditions in which the kidneys perform below the normal level for more than three months. Chronic kidney insufficiency is classified by five stages according to the decline in glomerular filtration rate and the degree of kidney damage (measured by the level of proteinuria). The most severe form is end-stage renal disease (chronic kidney failure) (Kidney Foundation: kidney disease outcome quality initiative, 2002). Year introduced: 2006	Chronic Kidney Disease - MeSH - NCBI
C-reactive protein	A plasma protein that circulates in increased amounts during inflammation and after tissue damage. C-reactive protein, measured by more sensitive methods often for coronary heart disease risk assessment, is referred to as high sensitivity c-reactive protein (hs-crp). Year introduced: 2006	C-Reactive Protein - MeSH - NCBI
Drug-eluting stent	Stents that are covered with materials embedded with chemicals that gradually release into the surrounding milieu. Year introduced: 2008	Drug-Eluting Stents - MeSH - NCBI
Minimal clinically important difference	A statistically significant minimum set of clinical outcomes that demonstrates a clinical benefit of an intervention or treatment. Year introduced: 2017	Minimal Clinically Important Difference - MeSH - NCBI
Myocardial infarction	Necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation). Year introduced: 1979	Myocardial Infarction - MeSH - NCBI
NLR (neutrophil-to-lymphocyte ratio)	"NLR reflects the dynamic relationship between innate (neutrophils) and adaptive cellular immune response (lymphocytes) during illness and various pathological states. NLR is influenced by many conditions, including age, race, medication, chronic diseases, like coronary heart disease, stroke, diabetes, obesity, psychiatric diagnosis, cancer of solid organs, anemia and stress."	(101)
Non-STEMI (non-ST-elevation myocardial infarction)	A myocardial infarction that does not produce elevations in the ST segments of the electrocardiogram (ECG). ST segment elevation of the ECG is often used in determining the treatment protocol (see also ST elevation for myocardial infarction). Year introduced: 2017	Non-ST Elevated Myocardial Infarction - MeSH - NCBI
PCI (percutaneous coronary intervention)	A family of percutaneous techniques used to manage coronary occlusion, including standard balloon angioplasty (percutaneous transluminal coronary angioplasty (PTCA)), the placement of intracoronary stents, and atheroablative technologies (e.g. atherectomy, endarterectomy, thrombectomy, percutaneous transluminal laser angioplasty). PTCA was the dominant form of PCI before the widespread use of stenting. Year introduced: 2013	Percutaneous Coronary Intervention - MeSH - NCBI

Table 1. Overview of the glossary of acronyms and definitions *(Continued)*

PCSK9 (proprotein convertase subtilisin/kexin type 9)	Agents that inhibit proprotein convertase subtilisin/kexin type 9 (see proprotein convertase 9 (PCSK9)), an enzyme that plays an important role in the degradation of the LDL receptors. It favours LDL catabolism and reduces plasma LDL-cholesterol. Year introduced: 2022	PCSK9 inhibitors - MeSH - NCBI
Sodium-glucose transporter 2 (SGLT2) inhibitors	Compounds that inhibit sodium-glucose transporter 2. They lower blood sugar by preventing the reabsorption of glucose by the kidney and are used in the treatment of type 2 diabetes mellitus. Year introduced: 2019	SGLT2 inhibitors - MeSH - NCBI
Stent thrombosis	The typical clinical presentation of ST consists of chest pain and ischaemic electrocardiographic changes in the target vessel territory. However, ST can also present as sudden death, or it can be asymptomatic in the setting of collateral vessels. The cornerstone of the angiographic detection of thrombus is the presence of a filling defect. When a filling defect is detected angiographically, intravascular ultrasound (IVUS) may be used to detect the underlying mechanism of ST (e.g. underexpansion, malapposition, edge dissection).	(102, 103)
STEMI (ST-elevation myocardial infarction)	A clinical syndrome defined by myocardial ischaemia symptoms; persistent elevation in the ST segments of the ECG; and release of biomarkers of myocardial necrosis (e.g. elevated troponin levels). ST segment elevation in the ECG is often used in determining the treatment protocol (see also non-STEMI). Year introduced: 2017	ST-Elevation Myocardial Infarction - MeSH - NCBI

Table 2. Overview of guideline-directed medical therapy in stable coronary artery disease

Category	Therapies/modifications Included
Antiplatelet therapy	Aspirin, clopidogrel, ticlopidine, ticagrelor, prasugrel, cangrelor
Lipid-lowering therapy	Statins (e.g. atorvastatin, rosuvastatin), ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors
Blood pressure control	Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers
Diabetes management	Glucagon-like peptide-1 receptor agonists, sodium-glucose transport protein inhibitors (as indicated for people with diabetes)
Angina relief	Nitrates, beta-blockers (see also blood pressure control), lifestyle counselling

Table 3. Overview of adverse events associated with guideline-directed medical therapy for stable coronary artery disease

Category	Adverse events
Antiplatelet Agents	
Aspirin	Gastrointestinal bleeding, peptic ulcers, allergic reactions, tinnitus (at high doses)

Table 3. Overview of adverse events associated with guideline-directed medical therapy for stable coronary artery disease *(Continued)*

Clopidogrel, ticagrelor	Bleeding (gastrointestinal, intracranial), thrombocytopenia, dyspnoea (ticagrelor)
Statins	
Common adverse events	Muscle pain (myalgia), liver enzyme abnormalities, gastrointestinal symptoms, increased risk of diabetes
Serious but rare events	Rhabdomyolysis, liver damage
Beta-blockers	
Common adverse events	Fatigue, cold extremities, depression, bradycardia, hypotension
Serious but rare events	Worsening of asthma/chronic obstructive pulmonary disease, heart block
Angiotensin-converting enzyme inhibitors	
Common adverse events	Cough, hyperkalemia, hypotension
Serious but rare events	Angioedema, kidney dysfunction
Angiotensin II receptor blockers	
Common adverse events	Dizziness, hyperkalemia, hypotension
Serious but rare events	Angioedema, kidney dysfunction
Calcium channel blockers	
Common adverse events	Oedema, constipation, dizziness, flushing
Serious but rare events	Bradycardia, heart block
Nitrates	
Common adverse events	Headache, flushing, hypotension, dizziness, reflex tachycardia
Serious but rare events	Tolerance
Source: reference # 24	

Table 4. Overview of the minimal clinically important differences for critical and important outcomes

Outcome	Proposed minimal clinically important difference	Meta-analyses and justification
Cardiovascular mortality	Absolute reduction ≥ 1.5% to 2%	• Zimmermann 2019: no significant differences in cardiovascular mortality were observed (40). • Navarese 2021: a 21% reduction in cardiovascular mortality was observed with PCI in long-term follow-up (RR 0.79, 95% CI 0.67 to 0.93) (42). • Barbarawi 2021: no significant differences in total or cardiovascular mortality were reported (34).

Table 4. Overview of the minimal clinically important differences for critical and important outcomes *(Continued)*

Non-fatal myocardial infarction (MI)	Absolute reduction ≥ 2% to 3%	• Soares 2021: PCI significantly reduced spontaneous myocardial infarction (OR 0.75, 95% CI 0.57 to 0.99, P = 0.04) (38). • Navarese 2021: PCI demonstrated a risk reduction in spontaneous MI (RR 0.74, 95% CI 0.64 to 0.86)(42). • Shah 2022: no reduction in overall MI was observed, but there were benefits in angina relief (37) .
Urgent revascularisation	Relative reduction (RRR) ≥ 20%	• Zimmermann 2019: FFR-PCI showed benefits in reducing urgent revascularisation (40). • Vij 2021: consistent benefits in reducing unplanned revascularisation were reported (39).
Severe bleeding	Acceptable absolute increase ≤ 1%	• Soares 2021 and Navarese 2021 mention procedural bleeding risks associated with PCI, but suggest acceptable rates (38). • Barbarawi 2021: periprocedural bleeding risks were documented but limited (34).

CI: confidence interval; FFR-PCI: fractional flow reserve-percutaneous coronary intervention; OR: odds ratio; RR: relative risk

This protocol will define the minimal clinically important difference to balance clinical relevance with the available evidence, acknowledging existing limitations. It will address the lack of GRADE assessments in many meta-analyses and the heterogeneity of their findings, which will require cautious interpretation. The minimal clinically important differences will act as provisional thresholds to guide decision-making while awaiting higher-quality evidence.

To ensure transparency, it will explicitly state the sources and ranges used to establish these minimal clinically important differences, highlighting their dependence on low-certainty evidence and adaptability to the baseline risk of the target population. Flexibility will be built into their application, allowing adjustments as evidence evolves and new data becomes available.

In doing so, the framework will remain practical, transparent, and aligned with emerging evidence, ensuring that the minimal clinically important differences serve as effective tools for clinical evaluation.