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Review

Effectiveness and Safety of Remote Ischemic Conditioning in People with Intermittent Claudication: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Introduction: Intermittent Claudication (IC), a painful manifestation of peripheral artery disease (PAD), is characterized by an imbalance between oxygen supply and demand in the lower limbs during physical activity and is associated with reduced walking capacity and health-related quality of life (HRQoL). Remote ischemic conditioning (RIC), a non-invasive intervention based on repeated cycles of limb ischemia and reperfusion, has been proposed to improve exercise tolerance in people with IC. However, the clinical effectiveness and safety of RIC in this population remain uncertain. **Methods and Analysis:** This protocol describes a systematic review and meta-analysis reported in accordance with the PRISMA-P statement. Electronic searches will be performed from 1986 to the most recent date prior to final analysis in MEDLINE, Embase, and CENTRAL. Eligible studies will include adults (≥18 years) with objectively confirmed PAD and IC, and classified as Rutherford categories 1–3 or Fontaine stages IIa–IIb. Participants with atypical claudication or with chronic limb-threatening ischemia will be excluded. Randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSIs) will be included and synthesized separately. RIC will be compared with sham (placebo) interventions. Primary outcomes will include walking distance and time, and adverse events (AEs). Secondary outcomes will include physiological measures and HRQoL. Two reviewers will independently perform study selection and data extraction. Risk of bias (RoB) will be assessed using the Cochrane RoB 2 tool for RCTs and ROBINS-I for NRSIs. Certainty of evidence will be evaluated using the GRADE approach. Intervention characteristics will be described using the TIDieR checklist. Where appropriate, random-effects meta-analyses will use mean differences or standardized mean differences for continuous outcomes and risk ratios or odds ratio for dichotomous outcomes. Where meta-analysis is not feasible, results will be synthesized following SWiM guidance. Heterogeneity, subgroup, sensitivity, and exploratory analyses will be performed where data permit. **Discussion:** This review will synthesize evidence on the effectiveness and safety of RIC in people with IC to inform clinical decision-making and future research regarding the potential role of RIC as a rehabilitation intervention. **Protocol registration:** PROSPERO CRD42024566595. **Funding:** Publication costs are covered by Physioswiss (Swiss Association of Physiotherapy, Bern, Switzerland).

Keywords: peripheral arterial disease; intermittent claudication; remote ischemic conditioning; walking performance; rehabilitation; adverse events; systematic review and meta-analysis

Introduction

Background

Peripheral artery disease (PAD) is a prevalent atherosclerotic condition characterized by progressive narrowing of peripheral arteries, leading to impaired blood flow, most commonly in the

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lower limbs [1]. It affects more than 236 million individuals worldwide [2] and its prevalence increases markedly with age [3–5]. PAD is associated with substantial morbidity and mortality, largely due to its strong association with systemic cardiovascular disease [5,6].

Intermittent claudication (IC) represents the most common symptomatic manifestation of PAD and is defined by exertional pain or discomfort in the lower limbs due to inadequate blood flow during exercise that is relieved by rest [1]. Approximately 10% of individuals with PAD develop IC during the course of the disease [4,7,8]. Beyond claudication symptoms, IC is associated with impaired walking performance, reduced functional independence and social participation, and diminished health-related quality of life (HRQoL) [9,10]. These limitations often result in reduced physical activity, leading to a sedentary lifestyle, which contributes to a cycle of deconditioning and increased cardiovascular risk.

Current management strategies for IC aim not only to reduce cardiovascular risk through lifestyle modification and pharmacological treatment, but also to improve walking and functional performance by enhancing exercise tolerance, which is a central determinant of independence and HRQoL [11].

Introduction to Remote Ischemic Conditioning (RIC)

Remote ischemic conditioning (RIC) is a non-invasive intervention consisting of repeated cycles of brief, transient limb ischemia followed by reperfusion, typically induced by inflating a blood pressure cuff on a limb at a pressure exceeding the individual's systolic blood pressure [12]. These ischemia–reperfusion cycles are applied at a site remote from the target tissue and are hypothesized to trigger systemic physiological and protective responses [12].

In PAD, non-invasive limb-based interventions such as intermittent pneumatic compression (IPC) have demonstrated beneficial hemodynamic effects [13–15]. In particular, several studies have shown increases in arterial blood flow, improved ankle–brachial index (ABI) (i.e., the ratio of ankle to brachial systolic blood pressure), pain reduction, and improved HRQoL in people with PAD [13–18]. These findings support the broader concept that externally applied, limb-based interventions can modulate lower-limb hemodynamics or HRQoL in people with IC, thereby providing a conceptual framework for investigating other non-invasive strategies such as RIC.

RIC differs fundamentally from IPC in both its physiological intent and proposed mechanisms of action. Rather than mechanically augmenting blood flow, it is hypothesized that repeated remote ischemia–reperfusion triggers systemic signals that may improve endothelial function and potentially skeletal muscle oxygen utilization, translating into improved exercise tolerance and walking performance [19–21]. This mechanism also raises safety considerations in a population with compromised limb perfusion, justifying explicit evaluation of adverse events (AEs) (e.g., skin irritation or injury, pain, bruising, numbness or paresthesia).

Consequently, RIC has been proposed as a potential adjunctive intervention to improve exercise tolerance and related clinical outcomes in people with IC. However, whether these hypothesized effects translate into meaningful improvements in walking performance, symptoms, or HRQoL has not been conclusively established.

Rationale for Systematic Review and Meta-Analysis

Improving walking and functional performance is a central therapeutic goal in people with IC, as these outcomes are closely linked to independence, HRQoL, and long-term cardiovascular health [22–24]. Although supervised exercise therapy is a cornerstone of care, many patients are unable to adhere to structured exercise programs [25–27], highlighting the need for additional, accessible, and non-invasive adjunctive interventions.

RIC has emerged as a potential adjunctive approach for people with IC. Several clinical studies have explored its effects on functional outcomes such as walking distance and time, and patient-reported measures [28–30]. However, the existing evidence is fragmented and characterized by

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substantial heterogeneity in RIC protocols and outcome measures. Individual studies are often small and may be underpowered to detect clinically meaningful effects when considered individually.

Furthermore, although RIC involves brief, controlled episodes of limb ischemia, the safety profile of repeated RIC application in people with IC has not been systematically evaluated. Given the underlying vascular pathology in this population, a structured synthesis of both clinical effectiveness and safety is warranted.

To date, no published systematic review with meta-analysis has comprehensively synthesized evidence on the clinical effectiveness and safety of RIC for clinically relevant outcomes (e.g., walking distance and time, HRQoL) in people with IC. A systematic review and meta-analysis is therefore warranted to integrate the existing data, quantify potential benefits and harms, explore sources of heterogeneity, and assess the certainty of the evidence to inform clinical practice and future research.

Objectives

The objective of this review is to systematically synthesize and, where appropriate, meta-analyze the clinical effectiveness of RIC compared with sham (placebo) intervention on clinically relevant outcomes in people with IC. Specifically, this review aims to:

1. Evaluate the clinical effectiveness of RIC on clinically relevant outcomes in people with IC.
2. Characterize the occurrence and nature of adverse events associated with RIC in this population.

Research Questions

- What is the clinical effectiveness of RIC, compared with sham (placebo), on clinically relevant outcomes in people with IC?
- What adverse events are associated with the application of RIC in people with IC when considering clinical use?

Method

Study Design

This protocol describes a systematic review and, where appropriate, meta-analysis evaluating the clinical effectiveness and safety of RIC in people with IC. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration ID: CRD42024566595) and was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [31].

Databases and Search Queries

A comprehensive electronic literature search will be conducted in MEDLINE (PubMed), Embase, and CENTRAL (Cochrane Library) from November 5, 1986, corresponding to the first description of ischemic preconditioning by Murry et al. [32], and will be updated prior to final analysis to capture newly published or registered studies.

Search strategies will be developed in accordance with PRISMA-S guidance to maximize sensitivity while maintaining reasonable precision [33]. Strategies will combine controlled vocabulary (e.g., MeSH terms) and free-text terms. Boolean operators, synonyms, and related terms will be used as appropriate. No methodological search filters (e.g., for study design) will be applied in order to maximize sensitivity. An example of the full search strategy will be reported in Table **Error! Reference source not found.**.

In addition, reference lists of included studies and relevant reviews will be screened for additional eligible studies. Grey literature sources will be searched to minimize publication bias, including clinical trial registries (e.g., ClinicalTrials.gov and the International Clinical Trials Registration Platform (ICTRP)), handsearching of conference proceedings and key journals in

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vascular medicine and rehabilitation, and other relevant sources. The search will be rerun within 3 months prior to manuscript submission to ensure the review reflects the most up-to-date evidence.

Eligibility Criteria

Randomized controlled trials (RCTs), including crossover and quasi-randomized designs, evaluating the effects of RIC in people with IC will be included. In addition, non-randomized studies of interventions (NRSIs) will be included to complement evidence on effectiveness and safety only where randomized evidence is limited or does not fully address the review questions [34]. Eligible NRSIs may include non-randomized controlled trials, cohort studies, and controlled before–after studies. Case series and uncontrolled before–after studies will be considered only for the assessment of AEs. Comparative AEs data from controlled studies (RCTs and NRSIs) will be synthesized separately from non-comparative evidence (e.g., case series and uncontrolled studies), which will be summarized descriptively as incidence proportions without causal attribution. Descriptive studies (e.g., qualitative studies, surveys), editorials, letters, expert opinions, and consensus statements will be excluded. Editorials, commentaries, and letters to the editor may nevertheless be consulted to identify additional relevant studies, clarify methodological issues, or contextualize findings, but will not contribute data to the synthesis. In accordance with Cochrane guidance, results from RCTs and NRSIs will not be pooled together, but will be synthesized separately, compared narratively, and interpreted cautiously because of their greater susceptibility to bias [35].

No restrictions will be applied based on language. Where necessary, non-English articles will be translated using modern translation tools (e.g., DeepL) and, if required, verified by a professional or a native speaker [36]. Any exclusions based on publication characteristics will be documented and justified during the study selection process.

Participants

Eligible participants will be adults aged 18 years or older with a clinical diagnosis of PAD, established by objective physiological assessment (e.g., resting ABI <0.90 or post-exercise ABI decrease consistent with PAD, toe–brachial index, or imaging evidence of PAD) [14] and presenting with IC [1]. Studies including participants classified as Rutherford categories 1 to 3 [37] or Fontaine stages IIa and IIb [38] will be eligible. A summary of the corresponding categories and stages is provided in Table **Error! Reference source not found.** for clarity.

Participants with atypical claudication due to non-vascular causes (e.g., spinal/root compression, arthritis, myopathies, peripheral neuropathies, psychogenic) [14] or with critical or chronic limb-threatening ischemia (Rutherford category ≥4 or Fontaine stage ≥ III) [39] will be excluded to reduce clinical heterogeneity and avoid populations with fundamentally different pathophysiology and management strategies.

Intervention and Comparator

Eligible interventions will include RIC and its temporal variants, including preconditioning (i.e., application of RIC before another intervention (e.g., physical exercise)), perconditioning (i.e., application of RIC during another intervention), and postconditioning (i.e., application of RIC after another intervention) [12]. RIC is defined as the application of repeated cycles of limb ischemia and reperfusion using an external cuff inflated to a pressure exceeding the individual's systolic blood pressure to achieve arterial occlusion, or using a fixed pressure threshold (e.g., 200 mmHg) [12,40].

Studies employing compression below systolic blood pressure (e.g., blood flow restriction training, IPC, medical flossing) will be excluded.

Eligible comparators will include sham (placebo) interventions. Sham (placebo) interventions must mimic the RIC procedure without achieving arterial occlusion (e.g., cuff applied without inflation or inflated to a pressure insufficient to occlude arterial inflow). In trials with multiple comparator arms, only data from RIC versus sham (placebo) groups will be extracted. All included

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studies must clearly describe the intervention and comparator used to ensure consistency across studies. In the absence of such information, the study authors will be contacted for clarification. Trials with unresolved ambiguity regarding the intervention or comparator will be excluded.

Outcome Measures

Primary outcomes will include: 1) walking distance measures such as pain-free walking (e.g., initial claudication distance, claudication onset distance), and maximal walking (e.g., maximum or peak walking distance, 6-Minute Walk Test, absolute claudication distance); 2) walking time measures such as pain-free walking (e.g., claudication onset time), and maximal walking (e.g., maximum or peak walking time); 3) adverse events, including serious adverse events, will be collected and synthesized when reported by study authors. The term adverse "events" will be used to refer to any unfavorable medical occurrences reported following RIC, irrespective of causal attribution.

Secondary outcomes will include: 1) physiological measures relevant to IC (e.g., ABI, peak exercise calf blood flow, transcutaneous oxygen pressure, or skin perfusion pressure); and 2) HRQoL assessed using validated instruments (e.g., SF-36, EQ-5D, VascuQol, ICQ).

Where outcomes are reported at multiple time points, data will be extracted at baseline and at the end of the intervention period (or, for single-session RIC, immediately post-session) for primary analyses. Follow-up outcomes will be grouped as short-term (≤4 weeks), medium-term (>4 to ≤12 weeks), and long-term (>12 weeks), where feasible, based on clinical relevance and data availability for secondary analyses [35].

Primary outcomes are direct indicators of functional capacity and improvement in people with IC and will drive the main conclusions and certainty assessments [14,24]. The assessment of AEs associated with the interventions is also crucial for evaluating the overall safety profile and risk–benefit ratio of the treatments [35]. The identification, extraction, and reporting of AEs will follow the PRISMA-Harms checklist to ensure transparent and comprehensive synthesis of safety outcomes [41]. Absence of reported AEs will not be interpreted as evidence of safety.

When multiple walking outcomes are reported, relevant core outcome sets (COS) to PAD and IC will be searched using the Core Outcome Measures in Effectiveness Trials (COMET) database, where available [42]. Otherwise, the measure most consistently reported across studies and based on clinical relevance will be prioritized to maximize comparability.

Secondary outcomes will provide additional information on the broader clinical effectiveness of interventions on the physiological mechanisms and on patient well-being. The selected outcomes reflect the multifaceted nature of IC and will be used to assess the overall effectiveness and safety of the interventions included in this review. Only outcomes pre-specified in this protocol will be considered primary or secondary outcomes for quantitative synthesis and certainty-of-evidence assessment [35]. Additional outcomes reported in included studies may be described narratively, but will be considered exploratory and will not inform the main conclusions or GRADE assessments. A summary of the inclusion and exclusion criteria is provided in Table **Error! Reference source not found.**.

Selection Process

All records retrieved from electronic searches will be imported into reference management software (e.g., Zotero or EndNote). Duplicates will be removed using automated deduplication tools (e.g., Automated Systematic Search Deduplicator (ASySD) tool, TERA-tool, or Rayyan) followed by manual verification to minimize erroneous removals. The deduplicated records will then be uploaded to a systematic review screening platform (e.g., Rayyan or Covidence).

Two reviewers will independently screen titles and abstracts against the pre-specified eligibility criteria, with reviewers blinded to each other's decisions within the platform. Records will be coded as "included", "excluded", or "uncertain". Prior to full–text screening, the eligibility criteria will be piloted on a sample of records (e.g., 50–100) to ensure consistent interpretation and refine decision

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rules, without reference to study results. The same independent process will be applied to full–text screening of potentially eligible records. Reasons for exclusion will be documented at the full-text stage.

The unit of interest for this review will be the study rather than individual reports. Where multiple reports of the same study are identified, these will be collated and linked, with data extracted across all relevant sources to avoid double counting and ensure completeness [35]. In cases of discrepant or conflicting information, the most complete and methodologically detailed source will be prioritized. Unresolved discrepancies will be clarified through correspondence with study authors where possible.

A PRISMA flow diagram will be used to transparently document the number of records identified, screened, assessed for eligibility, and included, along with reasons for exclusion at each stage. Disagreements between reviewers will be resolved through discussion. If consensus cannot be reached, a third independent reviewer will adjudicate. All decisions, amendments to decision rules, and resolutions of disagreements will be documented to ensure transparency and reproducibility.

Data Extraction and Study Characteristics

Two reviewers will independently extract data using a piloted, standardized extraction form. Discrepancies will be resolved through discussion or, if necessary, adjudication by a third reviewer. The extraction form will be refined after piloting on a small number of included studies, without using study results to guide changes.

For each extracted data item, the provenance of the information (e.g., journal article, trial registry entry, clinical study report, figure, or author correspondence) will be recorded to ensure traceability and transparency.

Extracted data will include: 1) study characteristics (e.g., authors, year of publication, country, funding source, protocol registration); 2) methodological characteristics (e.g., study design, inclusion and exclusion criteria, sample size, randomization procedures, time points of assessment, follow-up duration); 3) participant characteristics (e.g., age, sex, comorbidities, medication use, ABI, Rutherford category or Fontaine stage); 4) intervention and comparator characteristics (e.g., RIC temporal variants, limb used, frequency, intensity, number of cycles, intervention duration, cuff pressure, and sham (placebo) characteristics (e.g., no inflation vs. low inflation)); 5) outcome measures (e.g., walking distance and time, AEs, physiological measures, HRQoL); and 6) study results (e.g., effect sizes, means, standard deviations (SD), standard errors (SE), medians, confidence intervals (CI), p-values).

Additional study characteristics or intervention details considered relevant for interpretation or exploration of heterogeneity may also be extracted and will be explicitly reported as such.

AEs will be extracted verbatim from study reports and, where feasible, coded using the Medical Dictionary for Regulatory Activities (MedDRA) to allow standardized classification by system organ class and preferred term. AEs will be collected and reported systematically, with attention to definitions, severity, seriousness, attribution to the intervention, timing, and methods of collection (systematic versus non-systematic). Differences in AEs ascertainment methods across studies will be considered when interpreting and synthesizing safety data [35].

Where data are missing or unclear, corresponding study authors will be contacted. If data remain unavailable, pre-specified methods will be used to derive missing statistics (e.g., derivation of SD from SE, CI, p-values or extraction of data from figures). All extracted and derived numerical data will be cross-checked against the original sources to verify the direction and magnitude of effects, and to identify potential errors arising from data extraction, transformation, or conversion, in accordance with MECIR guidance [35]. The final analytic dataset will then be independently cross-checked by both reviewers to ensure internal consistency and accuracy. Sensitivity analyses will be conducted to assess the robustness of the findings to assumptions made during data derivation and handling of missing data.

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Risk of Bias (RoB) Assessment

Two reviewers will independently assess RoB for each critical outcome. Disagreements will be resolved by consensus or adjudication by a third reviewer, with justifications documented.

The effect of interest will be the effect of assignment to the intervention (i.e., intention-to-treat effect), where data allow. RoB due to deviations from intended interventions will therefore be judged with respect to the assignment effect. Where only per-protocol or as-treated analyses are reported, this will be explicitly documented and considered when interpreting the RoB and certainty of the evidence [35].

For RCTs, RoB will be assessed using the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) [35], covering five domains: 1) bias arising from the randomization process; 2) bias due to deviations from intended intervention; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result. Each domain and the overall judgment will be rated as "Low risk", "Some concerns", or "High risk".

For NRSIs, RoB will be assessed using the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool [35]. A target trial framework will be specified a priori to guide ROBINS-I assessments, including definition of the effect of interest and key confounders (e.g., baseline walking capacity, IC severity, ABI, comorbidities, and concomitant treatments). ROBINS-I covers seven domains: 1) bias due to confounding; 2) bias in selection of participants into the study; 3) bias in classification of interventions; 4) bias due to deviations from intended interventions; 5) bias due to missing data; 6) bias in measurement of outcomes; and 7) bias in selection of the reported result. Judgments will be rated as "Low", "Moderate", "Serious", or "Critical" RoB. Studies judged at "High risk" of bias (RoB 2) or "Critical" RoB (ROBINS-I) will not contribute to the primary quantitative synthesis. Their findings will be described narratively and may be included in sensitivity analyses to explore the influence of RoB on the results. Their limitations clearly highlighted to avoid misleading pooled estimates. RoB judgments will be summarized using structured tables and visual plots generated with dedicated visualization tools (e.g., robvis) to enhance transparency and interpretability. All assessments will be documented using RevMan web to ensure consistency and transparency.

Considerations regarding conflicts of interest in included studies will be examined using principles from the Tool for Addressing Conflicts of Interest in Trials (TACIT) framework, to support transparent consideration of how funding sources or investigator interests may influence study conduct, reporting, and interpretation [35].

Quality Assessment of Evidence

RoB assessments will directly inform the RoB domain of the GRADE certainty of evidence assessment for each critical outcome. RoB due to missing evidence (e.g., non-publication or selective non-reporting of outcomes) will be considered using principles from the Risk Of Bias due to Missing Evidence (ROB-ME) framework and incorporated within the GRADE publication bias where appropriate [43].

The certainty of evidence will be assessed only for outcomes prioritized a priori as critical for decision-making using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [34,43,44]. The GRADE approach assesses the quality of evidence in five domains: 1) RoB; 2) inconsistency; 3) indirectness; 4) imprecision; and 5) publication bias. For each outcome, certainty will be rated as "High", "Moderate", "Low", or "Very low", reflecting the degree of confidence that the true effect lies close to the estimated effect and is sufficient to inform decision-making. Certainty of evidence will be assessed separately for randomized and non-randomized evidence.

GRADE assessments will be conducted using GRADEpro software and summarized in a Summary of Findings (SoF) table. SoF tables will present relative and, where possible, absolute effects, together with the certainty of evidence for each critical outcome (e.g., walking capacity outcomes, AEs, and HRQoL) [35].

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Data Synthesis and Analysis

A structured descriptive synthesis of included studies will first be provided, summarizing participants, interventions, comparators, and outcomes (PICO). Intervention characteristics will be described using the Template for Intervention Description and Replication (TIDieR) checklist to enable reproducibility and to support exploration of clinical heterogeneity [45].

Where at least two studies addressing the same pre-specified PICO for synthesis are sufficiently similar, a meta-analysis will be conducted. Given expected clinical and methodological heterogeneity (e.g., variation in RIC protocols, and outcome assessments), random-effects models will be used as the primary analytical approach. The random-effects model will be interpreted as estimating the average intervention effect across a distribution of true effects. Between-study variance will be estimated using appropriate methods (e.g., Hartung-Knapp-Sidik-Jonkman adjustment), and results will be presented with 95% CI in forest plots. Meta-analyses will be performed using statistical software such as RevMan web or R.

For continuous outcomes, mean differences (MD) will be used when outcomes are measured on the same scale, and standardized mean differences (SMD) when different instruments measure the same construct. When SMD are used, scales will be oriented so that positive values consistently reflect benefit, and interpretation will consider the clinical meaning of standardized effects. For dichotomous outcomes, risk ratios (RR) or odds ratios (OR) will be calculated using methods suitable for sparse data where appropriate (e.g., Mantel-Haenszel method). For crossover trials, paired analyses will be used where within-participant data are available. When multiple walking outcomes are reported, outcomes included in relevant core outcome sets will be prioritized where available.

Statistical heterogeneity will be assessed using visual inspection of forest plots and quantitative statistics (e.g., Cochran's Q test, I^2 and τ^2), interpreted in conjunction with clinical and methodological considerations rather than rigid thresholds. Potential sources of heterogeneity will be explored using pre-specified subgroup analyses (e.g., RIC modality and temporal variants, sham (placebo) intervention characteristics, baseline IC severity), and meta-regression may be considered only when a sufficient number of studies (e.g., ≥10) is available and results will be interpreted cautiously as exploratory.

Sensitivity analyses will examine the robustness of findings, including exclusion of studies at high RoB and use of alternative statistical models (e.g., fixed-effects vs. random-effects) and applying alternative approaches for handling missing data, as recommended in the Cochrane Handbook (e.g., deriving SDs from SEs, confidence intervals, or p-values where required) [35].

Potential publication bias and small-study effects will be assessed where meta-analysis includes a sufficient number of studies (e.g., ≥10). Funnel plots may be visually inspected for asymmetry, and statistical tests for asymmetry (e.g., Egger's test) may be applied where appropriate. These methods will be interpreted cautiously, taking into account the number of included studies, between-study heterogeneity, and clinical diversity.

If funnel plot asymmetry is observed, potential sources of asymmetry will be explored, including publication bias, selective outcome reporting, and true heterogeneity. Where appropriate, exploratory methods (e.g., trim-and-fill) may be used to assess the potential impact of missing studies on pooled effect estimates, acknowledging the methodological limitations and assumptions underlying this approach.

Where quantitative synthesis is not appropriate due to substantial clinical or methodological heterogeneity (e.g., variation in RIC protocols, or outcome measures), results will be synthesized following the Synthesis Without Meta-Analysis (SWiM) guidance to ensure structured and transparent narrative and graphical synthesis [46].

Where appropriate, albatross plots may be used to explore overall patterns of statistical significance across studies by visualizing the relationship between p-values and approximate effect sizes when outcome measures are heterogeneous. For studies that do not report quantitative effect estimates, effect direction plots may be used to summarize the direction of effects (positive, negative, or no clear effect) for key outcomes, including walking distance and time, AEs, physiological

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measures, and HRQoL. Harvest plots may additionally be used to provide a qualitative synthesis of the evidence, grouping studies according to the direction and strength of reported effects while accounting for study characteristics such as design and RoB. This multi-method graphical synthesis will support a transparent and structured interpretation of the evidence when meta-analysis is inappropriate, without overstating certainty or implying quantitative precision.

Discussion

This systematic review and meta-analysis aims to synthesize evidence on the effectiveness and safety of RIC for clinically relevant outcomes in people with IC. By integrating data from RCTs and, where appropriate, NRSIs, this review will evaluate whether RIC is associated with meaningful improvements in functional outcomes and HRQoL, while also characterizing the occurrence and nature of AEs and relevant physiological outcomes.

Given the anticipated heterogeneity of RIC protocols, and outcome measures, this review will examine the consistency of findings across studies and formally assess the certainty of the evidence using established methodological frameworks. Randomized and non-randomized evidence will be considered separately to ensure appropriate interpretation of effectiveness and safety, with particular attention to methodological limitations and potential sources of bias. The balance between potential benefits and harms will be considered to support clinically relevant conclusions.

The findings of this review are expected to inform clinicians, researchers, and other stakeholders about the current evidence base and certainty of the findings regarding RIC as a potential adjunctive intervention in the management of IC. In addition, this synthesis will help identify key evidence gaps, sources of uncertainty, and methodological priorities to guide future clinical trials and implementation research in this field.

Abbreviations

ABI	ankle–brachial index
AEs	adverse events
HRQoL	health-related quality of life
IC	intermittent claudication
IPC	intermittent pneumatic compression
NRSIs	non-randomized studies of interventions
PAD	peripheral arterial disease
RIC	remote ischemic conditioning
RoB	risk of bias
SoF	summary of findings

Ethics Approval: Not applicable.

Consent of Participants: Not applicable.

Availability of Data and Materials: The datasets generated and/or analyzed during this systematic review will be made available in an open-access repository (e.g., Zenodo) upon publication. Additional materials, including extraction forms and analytic code where applicable, will be available from the corresponding author upon reasonable request.

Dissemination Plan: The results of this systematic review will be disseminated through publication in a peer-reviewed open-access journal. Findings will also be presented at relevant national and/or international scientific conferences.

Competing Interests: The author declares to have no financial, personal, social, commercial, academic, political, religious, professional, or institutional conflicts of interest.

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