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# Ranolazine in Chronic Stable Angina: A Systematic Review and Meta-Analysis

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## Abstract

Chronic stable angina (CSA) significantly impairs functional capacity and quality of life (QoL), with many patients remaining symptomatic despite standard treatment. Ranolazine, a late sodium current inhibitor, is utilized as an adjunctive antianginal therapy. This systematic review and meta-analysis evaluates its efficacy and safety in adult patients with CSA. We searched major databases through April 2025 for studies comparing ranolazine to placebo or standard therapy. Efficacy outcomes included angina burden, exercise parameters, QoL, and major adverse cardiovascular events (MACE), including myocardial infarction (MI) and revascularization. Safety was assessed via adverse event incidence. Data were synthesized using random-effects meta-analysis. Sixty-nine studies were included. Ranolazine significantly improved objective exercise measures, increasing exercise duration (mean difference {MD}, 33.1 seconds; 95% confidence interval {CI}, 27.3-38.9), time to angina onset (MD, 42.8 seconds; 95% CI, 34.2-51.5), and time to 1-mm ST depression (MD, 43.2 seconds; 95% CI, 33.8-52.6). Ranolazine was associated with a reduced risk of MI (risk ratio {RR}, 0.91; 95% CI, 0.84-0.98), coronary artery bypass grafting (CABG; RR, 0.55; 95% CI, 0.35-0.86), and any revascularization such as percutaneous coronary intervention (PCI) or CABG (RR, 0.77; 95% CI, 0.64-0.91). Adverse events were more frequent in the ranolazine group (RR, 1.45; 95% CI, 1.27-1.66) but were predominantly non-serious. Ranolazine provides robust symptomatic and functional benefits in patients with CSA. It is associated with modest reductions in MI and revascularization procedures, such as PCI or CABG. The data support ranolazine as an effective therapy for patients with CSA.

**Categories:** Cardiology
**Keywords:** angina, cardiovascular disease, chronic stable angina, myocardial infarction, ranolazine

## Introduction And Background

Chronic stable angina (CSA) remains a significant global health concern and is one of the most common clinical manifestations of coronary artery disease (CAD) [1]. It is characterized by episodes of chest discomfort or pain triggered by emotional stress or physical exertion, typically relieved by rest or the administration of short-acting nitrates. Although not immediately life-threatening, CSA imposes a substantial burden on patients' daily functioning, quality of life (QoL), and psychological well-being [1,2]. The effective management of angina is crucial for reducing symptom burden, improving functional capacity, and potentially preventing the progression of ischemic heart disease.

Ranolazine, a novel antianginal agent, acts by selectively inhibiting the late sodium current in myocardial cells, thereby reducing intracellular calcium overload and improving myocardial relaxation and perfusion [3]. Unlike traditional antianginal drugs, ranolazine does not significantly affect heart rate or blood pressure, making it a potentially attractive option, particularly for patients who are intolerant to or inadequately controlled by conventional therapies [4]. Over the past two decades, several studies (including trials and observational studies) have evaluated the efficacy and safety of ranolazine in CSA, using a range of clinical and patient-reported outcomes such as exercise tolerance, the frequency of angina episodes, nitrate use, Seattle Angina Questionnaire (SAQ) scores, and major adverse cardiovascular events (MACE). Nevertheless, variability persists in the reported effectiveness of ranolazine, with differences in study designs, follow-up durations, population characteristics, and outcome measures. While several studies suggest that ranolazine offers meaningful benefits in improving angina symptoms and functional parameters, others report modest or inconclusive results. Additionally, some studies report outcomes narratively or present data in formats that preclude quantitative synthesis, highlighting the need for a comprehensive assessment [5].

Therefore, we conducted this systematic review and meta-analysis to evaluate the safety and efficacy of ranolazine in adult patients with CSA. By integrating evidence from randomized trials, non-randomized studies, and real-world data, we provide the most comprehensive assessment to date of its impact on clinical and patient-centered outcomes, aiming to clarify its role in the management of CSA and to inform clinicians, researchers, and policymakers in evidence-based decision-making.

# Review

## Methods

We adhered to the PRISMA 2020 reporting standards in conducting and presenting this systematic review and meta-analysis [6]. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420251051059).

### *Eligibility Criteria*

We included original studies involving adult patients (≥18 years) with CSA that quantitatively evaluated the use of ranolazine compared to standard therapy, placebo, or other antianginal agents. Eligible studies assessed outcomes that captured reductions in symptom burden (e.g., SAQ scores and the use of short-acting nitrates), improvements in functional capacity (e.g., exercise duration and time to angina), and the prevention of ischemic heart disease progression (e.g., the incidence of MACE, myocardial infarction {MI}, percutaneous coronary intervention {PCI}, and coronary artery bypass grafting {CABG}). Safety outcomes of ranolazine included the incidence of adverse events. We included randomized controlled trials (RCTs), non-randomized interventional studies, and observational studies (cohort or case-control designs). Studies without extractable quantitative data (e.g., lacking measures of effect, standard deviations, or sample sizes) were included in the narrative synthesis only, provided they reported relevant outcomes. We excluded studies involving pediatric populations, animal or in vitro studies, reviews, case reports, editorials, and conference abstracts lacking full data.

### *Search Strategy*

A systematic search of Medical Literature Analysis and Retrieval System Online (MEDLINE) (via PubMed), Excerpta Medica database (EMBASE), Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted from inception to April 2025. Additional sources included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and hand-searching reference lists of included studies and relevant reviews. The search combined Medical Subject Headings (MeSH) and free-text terms for "ranolazine." We did not include additional search terms to maximize search sensitivity. No language or date restrictions were applied.

### *Study Selection*

All identified records were imported into Rayyan (Rayyan Systems Inc., Cambridge, MA) for deduplication and initial screening [7]. Two authors independently reviewed titles and abstracts and subsequently assessed the full texts of potentially relevant articles. Differences in judgment were resolved by discussion, and a third reviewer was consulted when consensus could not be reached. Studies providing quantitative outcome data were included in the meta-analysis, while those meeting inclusion criteria but lacking extractable data were incorporated into the narrative synthesis.

### *Data Extraction*

Data were independently extracted by two reviewers using a pre-piloted standardized form. Extracted information included study characteristics (author, the year of publication, country, study design {RCT, non-randomized trial, and other observational designs}, setting, sample size in intervention and control groups, population type, and the inclusion of special subgroups such as patients with diabetes or elderly patients). Participant characteristics, including mean age, sex distribution, comorbidities, a history of prior revascularization (PCI or CABG), and ranolazine dosage, were also collected. Outcome data included measures related to PCI requirements, angina symptom scores, QoL scores, exercise tolerance, and other relevant endpoints. Outcomes were recorded as reported in the original studies, as either means or frequencies, along with any covariates used for adjustment. A third reviewer audited the extracted data for consistency.

### *Risk of Bias Assessment*

Two reviewers independently evaluated the risk of bias in the included studies. For RCTs, assessment was carried out using the Cochrane Risk of Bias 2 (RoB 2) tool, which examines potential bias related to randomization, deviations from intended interventions, incomplete outcome data, outcome measurement, and selective reporting [8]. Non-randomized interventional studies were appraised with the ROBINS-I tool, which considers confounding, participant selection, intervention classification, deviations from intended

interventions, missing data, outcome assessment, and reporting bias [9]. Any disagreements were resolved by consensus, with a third reviewer consulted when necessary. Each study was subsequently rated as low, moderate, or high risk of bias according to predefined criteria.

*Statistical Analysis*

Random-effects meta-analyses were conducted using the "meta" package in R version 4.4.3 [10]. The restricted maximum likelihood estimator method was used to estimate the between-study variance: $\tau^2$. For studies with multiple follow-up assessments, the latest follow-up data were used. Continuous outcomes such as SAQ scores in different domains (angina frequency, angina stability, physical limitation, QoL, and treatment satisfaction), exercise duration, time to angina onset, time to 1-mm ST depression, and angina frequency were pooled as mean differences (MDs) with 95% confidence intervals (CIs). Dichotomous outcomes such as the incidence of MI, revascularization (PCI and CABG), and hospitalization were summarized using risk ratios (RRs) with 95% CIs. Heterogeneity across studies was assessed using the $I^2$ statistic, with $I^2$ values greater than 75% considered indicative of substantial heterogeneity [11]. Forest plots were generated for all pooled estimates to assess effect sizes and CIs visually [12]. Subgroup analyses were conducted based on the follow-up duration of more than six months and on disease subtypes (obstructive or microvascular) to evaluate the effects of ranolazine. Sensitivity analysis was performed by omitting studies with a high risk of bias.

*Publication Bias and Certainty of Evidence*

Potential publication bias was explored through the visual examination of funnel plots and confirmed with Egger's regression test, using a significance threshold of $p < 0.10$ wherever the number of studies available was more than 10. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, and a summary of findings table was generated with GRADEpro Guideline Development Tool (GDT) (Evidence Prime, Hamilton, Canada; 2023, available from gradepro.org).

## Results

*Literature Search*

Our search strategy identified 6033 unique records, including 1227 from PubMed, 1252 from EMBASE, 1702 from Web of Science, 190 from the Cochrane Central Register of Controlled Trials, and 1662 from Scopus. After removing 3161 duplicate entries, 2872 records remained for title and abstract screening. Of these, 2743 were excluded because they did not meet the predefined eligibility criteria related to the study population, intervention, comparator, or outcomes. The full texts of the remaining 129 articles were sought for retrieval and detailed assessment. Of these, 115 were finally retrieved, while 14 were not retrieved as they did not match the specified publication type. Upon full-text review, 46 studies were excluded: 11 were conference abstracts of the main study, six did not evaluate ranolazine, eight were review articles, six did not match the publication type, six assessed different outcomes, four did not match the population in question, four were of varying study designs, and one was a duplicate entry. Ultimately, 69 studies met all inclusion criteria and were included in the final synthesis. Among these, data from 40 studies were used for quantitative meta-analysis of different outcomes (Figure *1*).

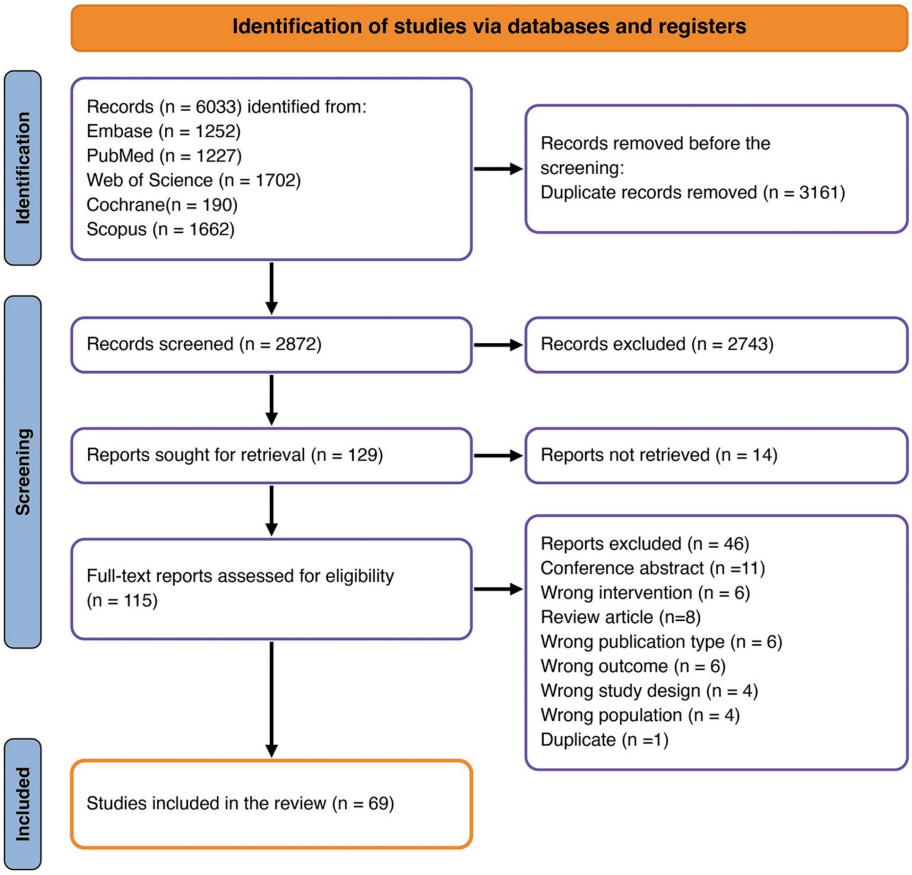



**FIGURE 1: Flowchart depicting article selection and screening process**

*Characteristics of the Included Studies*

The included studies assessing the efficacy and safety of ranolazine in patients with various forms of angina and ischemic heart conditions were diverse in design, population, and setting. Among them, a mix of RCTs, non-randomized controlled trials, cohort studies, prospective observational studies, retrospective analyses, and case series was identified. Geographically, most studies were conducted in the USA and Europe, with additional contributions from countries such as Brazil, India, Pakistan, Canada, and Russia. Sample sizes varied widely, ranging from as few as seven participants to over 19000 in large database cohort analyses. The participant populations predominantly included patients with CSA, microvascular angina, non-obstructive CAD, coronary microvascular dysfunction, or refractory angina, often on background antianginal therapy and frequently having undergone prior revascularization procedures such as PCI or CABG. The average participant age ranged from 50 to 75 years, with most studies reporting a higher proportion of male participants; however, several recent trials focused specifically on female populations or those with gender-balanced recruitment. Special groups included patients with diabetes mellitus, those with incomplete revascularization, and those with documented coronary flow reserve (CFR) abnormalities. The characteristics of the included studies are summarized in Table *1*.

| Author year | Design | Country | Participants (intervention) | Participants (control) | Population | Mean age | Gender (% male) | Dose of ranolazine | Follow-up duration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| Storey et al., 2020 [13] | Prospective registry | USA | 158 | 158 | Refractory angina, high cardiac risk | 64 | 73% | 500 mg BID, titrated to 1000 mg BID | 3 years | SR |
| Alexopoulos et al., 2016 [14] | Cohort | The Netherlands | 189 | 189 | Chronic stable angina, 56.6% prior revascularization | 71.5 | 70.4% | 375 mg BID, >500/750 mg BID | 6 months | CCS, SLN use |
| Dourado et al., 2022 [15] | Retrospective, pre-post | Brazil | 9 | 10 | Refractory angina (CCS 3/4), ≥3 antianginals | 61 | NA | 500 mg BID | 3 months | CCS, QTc |
| Villano et al., | RCT | USA | 15 | 15 | Stable microvascular angina, | NA | NA | 375 mg BID | 4 weeks | Angina frequency, stability, physical limitation, QoL, Tx |

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| 2013 [16] | | | | | CFR < 2.5 | | | | | satisfaction, exercise, ST depression, RPP |
| Willis et al., 2019 [17] | RCT | USA | 13 | 16 | CCS | 68 | CCS | 500 mg BID × one week >1000 mg BID | 14 weeks (two-week titration + 12-week exercise training) | Angina frequency, angina stability, physical limitation, quality of life, treatment satisfaction |
| Alexander et al., 2016 [18] | RCT | USA | 1207 | 1182 | Chronic angina, post-PCI ICR | 63 | 80% | 1000 mg BID | 12 months; median of 643 days | Angina frequency, stability, physical limitation, QoL, Tx satisfaction |
| Page et al., 2015 [19] | Cohort | USA | 2002 | 2002 | Chronic stable angina, some with DM | 66 | 63% | NR | 12 months | SR |
| Stone et al., 2010 [20] | RCT | USA | 170 | 170 | Stable ischemic heart disease, exertional angina | ≥21 | NR | 500, 1000, 1500 mg BID (one week each) | 4 weeks | SR |
| Chaitman et al., 2004 [21] | RCT | USA | 191 | 191 | Chronic severe stable angina | 64.3 | 73.3% | 500, 1000, 1500 mg BID (one week each) | 1 week/dose; 2-year open-label | Exercise, angina, ST depression |
| Rambarat et al., 2019 [22] | RCT | The Netherlands | 81 | 81 | Symptomatic, non-obstructive CAD, CFR < 2.5 | 55 | 1.2% | 500 mg BID (one week), then 1000 mg BID | 6 weeks (two weeks, ranolazine; two-week washout; two weeks, placebo) | SR |
| Sinha et al., 2024 [23] | RCT | USA | 40 | 47 | ANOCA, some CMD | 61 | 38% | 375 mg BID (one week), then 500/750 mg BID | 9 weeks (four weeks, ranolazine; one-week washout; four weeks, amlodipine) | SR |
| Borzi et al., 2018 [24] | Prospective, pre-post | USA | 94 | 94 | SCAD (73% COAD; 27% NOCAD), symptomatic despite BB/CCB | 69 | 68% | 375-500 mg BID | 6 months | Angina frequency, stability, physical limitation, QoL, Tx satisfaction |
| Tolunay, 2021 [25] | Non-RCT | England | 30 | 30 | CAD with angina | 68.35 | 55% | 750 mg BID, then 1000 mg/day | 1 month | SR |
| Rayner-Hartley et al., 2020 [26] | Retrospective, pre-post | USA | 31 | 31 | Microvascular angina, severe refractory, no obstructive CAD | 57 | 23% | 500-2000 mg daily | ~6 weeks (median of 17 months) | SR |
| Koh et al., 2020 [27] | RCT | USA | 11 | 11 | Angina, NOCAD, 54.5% CFR < 2.0 | NR | NR | 500 mg BID (two weeks), then 1000 mg BID | 12 weeks | Angina frequency, stability, physical limitation, QoL, Tx satisfaction, CFR |
| Caminiti et al., 2016 [28] | RCT | The Netherlands | 20 | 20 | Overweight/obese nondiabetic CHD, insulin resistance | 62.4 | 77.5% | 500 mg BID | 12 weeks | SR |
| Mehta et al., 2019 [29] | Open-label, pre-post | USA | 159 | 159 | Women with IHD, ≥2 angina episodes/week | 65 | 0% | 500 mg BID | 4 weeks | SR |
| Ahmed et al., 2017 [30] | Open-label, pre-post | USA | 7 | 7 | Type 1 CMVD, non-obstructive CAD, HTN, DLP | 57.6 | 57% | 500 mg BID (seven days), then 1000 mg BID | 4 weeks | CFR |
| Safdar et al., 2017 [31] | RCT | USA | 21 | 10 | Chest pain, CMD | 50 | 29% | 500 mg BID (one week), then 1000 mg BID | 30 days | CFR |
| Zweiker et al., 2019 [32] | Prospective cohort | Austria | 289 | 292 | Stable angina, 57.2% prior revascularization | 73.6 | 55.5% | 375 mg BID, titrated to 500/750 mg BID | 12 weeks | Angina frequency, SLN use |
| Bress et al., 2018 [33] | Retrospective cohort | USA | 4770 | 32290 | Veterans with chronic stable angina | 67 | 98% | NR | Median of 3.4 years | MI, PCI, CABG |
| Shah et al., 2017 [34] | RCT | England | 21 | 19 | Diabetic, non-obstructive CAD, 43% prior revascularization | 64 | 51% | 500 mg BID (one week), then 1000 mg BID | 8 weeks (four weeks, ranolazine; three-day washout; four weeks, placebo) | SR |
| Phelps et al., 2012 [35] | Cohort | USA | 881 | 3664 | Angina, changed antianginal therapy | 61 | NR | NR | 12 months | PCI, CABG, revascularization, hospitalization, SLN |
| | | | | | | | | 500 mg BID (seven | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| Weisz et al., 2016 [36] | RCT | England | 1332 | 1319 | Chronic angina, post-PCI ICR | 63.4 | 79% | days), then 1000 mg BID | Median of 643 days | MI, hospitalization, cardiac death, AE, mortality, any revascularization |
| Tagliamonte et al., 2015 [37] | RCT | USA | 29 | 29 | Angina, non-obstructive CAD | 66 | 67% | 375 mg BID (four weeks), then 500 mg BID | 8 weeks | Angina frequency, stability, physical limitation, QoL, Tx satisfaction, ECG frequency |
| Meyer et al., 2019 [38] | Retrospective cohort | USA | 19574 | 89167 | SIHD | 67 | 59% | NR | 12 months | MACE any revascularization |
| Kanorskii and Smolenskaya, 2016 [39] | RCT | Russia | 53 | 54 | Coronary heart disease and functional class II/III stable angina | NR | NR | 500 mg BID | 6 months | SR |
| Gutierrez et al., 2015 [40] | RCT | USA | 1317 | 1334 | Chronic angina with non-ST-elevation acute coronary syndrome post-PCI | NR | NR | IV 200 mg bolus, 80 mg/hour (12-96 hours), then 1000 mg BID oral | 12 months | MACE, MI, cardiac death, hospitalization, any revascularization |
| Greene et al., 2012 [41] | Case-series | USA | 18 | 18 | Men with ≥3 angina episodes/week despite max therapy | 66 | 100% | 500 or 1000 mg BID | 2-12 weeks | ECG for angina weekly, QTc |
| Mehta et al., 2011 [42] | RCT | USA | 20 | 20 | Women with ischemia, no obstructive CAD, abnormal CMR | 65 | 0% | 500 mg BID (two weeks), then 1000 mg BID | 10 weeks (four-week treatment; two-week washout) | Angina frequency, stability, physical limitation, QoL, Tx satisfaction |
| Muhlestein and Grehan, 2013 [43] | Cross-sectional, pre-post | New Zealand | 1785 | 1775 | Chronic angina, no prior revascularization | 64 | 36 | NR | Not applicable (recall-based) | SR |
| Bennett et al., 2014 [44] | Cohort | USA | 100 | 43 | Refractory angina clinic patients | 64.1 | 75 | 500 mg BID, titrated to 1000 mg BID | 12 months | SR |
| Wilson et al., 2009 [45] | RCT | USA | 1789 | 1776 | Chronic angina with ACS (MERLIN-TIMI 36) | NR | NR | IV for 12-96 hours, then 1000 mg BID oral | Median of 350 days | ECG exercise duration, MACE overall, MACE all mortality, time 1-mm ST depression |
| Deshmukh et al., 2009 [46] | RCT | England | 27 | 27 | CAD, post-CABG/PCI, CCS class I angina | 64 | 70 | 500 mg BID (one week), then 1000 mg BID | 12 weeks (six weeks per treatment) | SR |
| Karwatowska-Prokopczuk et al., 2013 [47] | RCT | England | 6492 | 3256 | Non-ST-elevation acute coronary syndrome at moderate-to-high risk for recurrent ischemic events | 63 | NR | IV, then 1000 mg BID oral; 500 mg if renal impairment | Median of 348 days | SR |
| Reeder et al., 2012 [48] | Cohort | USA | 35 | 35 | Veterans with chronic stable angina | 67.8 | 100% | 500 mg BID, titrated to 1000 mg BID | 3 months | SAQ (angina frequency, physical limitation, Tx satisfaction, QoL, stability), adverse events, cardiac death |
| Olympios et al., 2024 [49] | Non-RCT | Switzerland | 1101 | 1101 | Adults with angina, recently started on ranolazine | 71.3 | 73.29% | 375 mg BID | 3 months | SLN use, angina frequency, CCS, time to angina, QoL, discontinuation |
| Khot et al., 2017 [50] | RCT | India | 72 | 72 | Chronic stable angina, ≥2-3 episodes/week | 58.74 | 72.2% | 500 mg BID or 1 g OD | 6 months | Angina frequency, exercise (TMT), ECG, SAQ, stress ECG |
| Shammas et al., 2015 [51] | RCT | New Zealand | 24 | 25 | Ischemic cardiomyopathy, angina/dyspnea, LVEF ≤ 40% | 71.5 | 82.1% | 500 mg BID (one week), then 1000 mg BID | 16 weeks | SAQ, dyspnea (RDS) |
| Lee et al., 2025 [52] | RCT | Singapore | 38 | 35 | CAD, stable angina ≥ 3 months | 60.4 | 100 | 500-1000 mg BID | 12 weeks | Time to angina, ST depression, SLN use, angina frequency, ETT, laboratory parameters, AEs |
| Calcagno et al., 2020 [53] | RCT | Switzerland | 49 | 49 | CAD, post-PCI, CCS II/III angina | 62.6 | 89.8% | 375 mg BID | 30 days | Exercise, time to angina, RPP |
| Rahmani et al., 2022 [54] | RCT | Canada | 31 | 31 | Post-stent, persistent angina | 58.81 | 59.68% | 1000 mg daily | 4 weeks | Exercise, chest pain severity |

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|---|---|---|---|---|---|---|---|---|---|---|
| Murray and Colombo, 2016 [55] | Cohort | USA | 51 | 54 | Chronic disease patients | 64.51 | 74.29% | 500-1000 mg BID | 6.19 years | Cardiac death, MI, PCI, CABG, revascularization, AEs, ACS, MPI, RFa, CAN |
| Birkeland et al., 2017 [56] | RCT | Canada | 16 | 24 | Ischemia, no obstructive CAD, CMD | 54.3 | 3% | 500 mg BID (one week), 1000 mg BID (three weeks) | 2 weeks | SAQ (angina frequency, physical limitation, Tx satisfaction, QoL, stability), RPP, MPRI |
| Chaturvedi et al., 2013 [57] | RCT | India | 30 | 31 | Chronic stable angina, 18-60 years | 60.3 | 88.3% | 500 mg BID | 8 weeks | Angina frequency, AEs, BP, HR, hematological, biochemical |
| Khalil-ur-Rehman et al., 2017 [58] | Non-RCT | Pakistan | 53 | 53 | Angina, increased chest pain frequency | NR | 100% | 750 mg BID | 6 weeks | Angina frequency, SLN use, pain duration, hemodynamics, ECG, laboratory parameters, AEs |
| Jain et al., 1990 [59] | RCT | England | 14 | 14 | Stable effort-induced angina, 3-10-minute exercise | 59.9 | 78.57% | 30 mg TID, then 60 mg TID | 6 weeks | Exercise, time to angina, ST depression, RPP, angina frequency, GTN use, AEs |
| Cocco et al., 1992 [60] | RCT | Switzerland, Belgium | 52 | 52 | Chronic stable angina, symptomatic despite BB/diltiazem | NR | NR | 10, 60, 120, 240 mg | NR | Exercise, time to angina, ST depression, plasma levels, hemodynamics |
| Singh et al., 2014 [61] | RCT | England | 61 | 61 | Stable CAD | 62 | 69% | 500 mg BID | 6 months | ETT, HbA1c, angina scores, lipids, BMI, AEs |
| Sendón et al., 2012 [62] | RCT | Spain | 174 | 84 | CAD, chronic exertional angina, max therapy | 65.3 | 82.6% | 750 or 1000 mg BID | 12 weeks | Exercise, time to angina, ST depression, RPP, AEs |
| Thadani et al., 1994 [63] | RCT | USA | 240 | 79 | Chronic stable angina, ECG ischemia | 65.26 | 79% | 30, 60, 120 mg TID | 4 weeks | Exercise, time to angina, ST depression, RPP, GTN use, angina episodes |
| Kosiborod et al., 2013 [64] | RCT | USA, Israel | 462 | 465 | T2DM, CAD, symptomatic angina | 64 | 61% | 500 mg BID (one week), then 1000 mg BID | 12 weeks | MI, AEs, SLN use, angina frequency, mortality |
| Stone et al., 2006 [65] | RCT | USA, Russia | 281 | 284 | CAD, ≥3 angina episodes/week despite amlodipine | 61.65 | 72.5% | 500 mg (one week), then 1000 mg BID | 6 weeks | SLN use, angina frequency, MI, AEs, SAQ, hemodynamics, ECG |
| Rousseau et al., 2005 [66] | RCT | USA, Belgium, Switzerland | 158 | 158 | Chronic angina pectoris | 59 | 89% | 400 mg TID | 1 week | AEs, time to angina, exercise, ST depression, hemodynamics |
| Morrow et al., 2007 [67] | RCT | Multiple | 3279 | 3281 | Non-ST-elevation ACS | 64 | 65.1% | 1000 mg BID after IV loading | Median of 348 days | SAQ-angina frequency, cardiac death, MI, revascularization, mortality, hospitalization, AEs |
| Koren et al., 2007 [68] | RCT | USA | 746 | 746 | Severe chronic stable angina | <65 | 77.7% | 500, 750, 1000 mg BID | Mean of 2.82 years | Safety, ranolazine intolerance, mortality |
| Venkataraman et al., 2009 [69] | NR | USA | 21 | 21 | CAD, ischemia on SPECT MPI | 65 | 67% | 1000 mg BID | 4 weeks | Exercise, MPI, perfusion defects, angina, QT, LVEF |
| Patel et al., 2015 [70] | RCT | England | 50 | 50 | Refractory angina despite revascularization, therapy | 65.2 | 87% | 375 mg BID | 1 month | CCS, SLN use, AEs, QTc, 6MWD, GTN use |
| Pylova and Tseluyko, 2022 [71] | RCT | Ukraine | 16 | 37 | Ischemia, no obstructive CAD | 57 | 33.9% | 1000 mg BID | 6 months | Exercise, RPP, ventricular arrhythmias |
| Kuchmin et al., 2018 [72] | RCT | USA, Russia | 21 | 21 | SIHD with diastolic dysfunction | | | 1000 mg BID | 4 weeks | Diastolic function, E/A ratio, DT, IVRT |
| Ling et al., 2013 [73] | Cohort | USA | 150 | 150 | Refractory angina resistant to therapy/revascularization | 66 | 64% | 860 ± 278 mg/day to 1616 ± 526 mg/day | 12 months | MI, PCI, CABG, hospitalizations, CCS, AEs |
| Malhotra et al., 2019 [74] | RCT | USA | 11 | 16 | SIHD, angina, deferred PCI (FFR ≥ 0.81) | NR | NR | 1000 mg BID | NR | SLN use, physical activity, MVPA, steps/day, SIHD guidelines |
| Coleman et al., 2018 [75] | RCT | USA | 457 | 461 | T2DM, chronic stable angina | NR | NR | 500 mg BID (one week), then 1000 mg BID | 8 weeks | SF-36 physical/mental health, domain scores |

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|---|---|---|---|---|---|---|---|---|---|---|
| Bavry et al., 2017 [76] | RCT | USA | 25 | 25 | Chronic stable angina, myocardial ischemia | 67 | NR | 500 mg BID (one week), then 1000 mg BID | 16 weeks | SAQ (angina frequency, physical limitation, Tx satisfaction, QoL, stability), ischemia-driven events |
| Bairey Merz et al., 2016 [77] | RCT | USA | 70 | 72 | Ischemia, no obstructive CAD, abnormal CRT/CMRI | 55.2 | 4% | 500 mg BID (one week), then 1000 mg BID | 2 weeks | SAQ (angina frequency, physical limitation, Tx satisfaction, QoL, stability), angina frequency, SLN use, MPRI |
| Egea-Serrano et al., 2018 [78] | RCT | Spain | 7 | 7 | Angina, non-obstructive CAD | 65 | 57.14% | 375 mg BID | 3 months | CFR, functional capacity, MetS, safety |
| Timmis et al., 2006 [79] | RCT | UK | 554 | 269 | Diabetic, chronic stable angina (CARISA subset) | 64.22 | 77.4% | 750 and 1000 mg BID | 2 years | Exercise, time to angina, ST depression, SLN use, angina frequency, HbA1c, glucose, lipids |
| Chaitman et al., 2004 [80] | RCT | USA | 554 | 269 | Chronic stable angina, symptomatic | 63.97 | 77.5% | 750 and 1000 mg BID | 12 weeks | Exercise, time to angina, ST depression, ECG ischemia, safety |
| Pepine and Wolff, 1999 [81] | RCT | USA | 159 | 159 | Chronic stable angina, responsive to therapy | 64.2 | 72% | 267 mg TID, 400 mg BID/TID | 5 weeks | Time to angina, exercise, ST depression, plasma levels, hemodynamics, safety |

**TABLE 1: Comprehensive overview of the included studies**

ACS, acute coronary syndrome; AE, adverse event; ANOCA, angina with non-obstructive coronary arteries; BB, beta-blocker; BID, twice per day; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAN, coronary artery narrowing; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; CHD, coronary heart disease; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; CMR, cardiac magnetic resonance; CMVD, coronary microvascular disease; COAD, coronary obstructive artery disease; CRT, cardiac resynchronization therapy; DLP, dyslipidemia; DM, diabetes mellitus; DT, deceleration time; E/A, early-to-late diastolic transmitral flow velocity ratio; ETT, exercise tolerance test; GTN, glyceryl trinitrate; HbA1c, glycosylated hemoglobin; HR, heart rate; ICR, incomplete coronary revascularization; IHD, ischemic heart disease; IVRT, isovolumic relaxation time; LVEF, left ventricle ejection fraction; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; MI, myocardial infarction; MPI, myocardial perfusion imaging; MPRI, myocardial perfusion reserve index; MVPA, moderate-to-vigorous physical activity; NA, not available; NOCAD, non-obstructive coronary artery disease; NR, not reported; OD, once daily; PCI, percutaneous coronary intervention; QoL, quality of life; QTc, corrected QT; RCT, randomized controlled trial; RDS, Rose Dyspnea Scale; RFa, radiofrequency ablation; RPP, rate–pressure product; SAQ, Seattle Angina Questionnaire; SCAD, stable coronary artery disease; SF-36, 36-Item Short Form Survey; SIHD, stable ischemic heart disease; SLN, sublingual nitroglycerin; SPECT, single-photon emission computed tomography; SR, symptom relief; T2DM, type 2 diabetes mellitus; TID, three times a day; TMT, treadmill test; Tx, treatment; 6MWD, six-minute walk distance

*Risk of Bias Across Included Studies*

Randomized studies: Risk of bias in RCTs was assessed with the RoB 2 tool across five domains (Figure *2*). Overall, most trials were judged to have a low-to-moderate risk of bias. The primary concern was the randomization process, particularly the limited details provided on sequence generation and allocation concealment. In contrast, deviations from intended interventions and selective reporting were typically considered low risk. Missing outcome data and outcome measurement presented greater variability, with several studies rated at high risk, reflecting incomplete follow-up and potential detection bias. Overall, while several studies were assessed as low risk, a considerable proportion raised some concerns, particularly related to randomization procedures and outcome measurement. Nevertheless, the consistency of effect estimates across trials suggests that these risks are unlikely to have materially influenced the pooled findings.

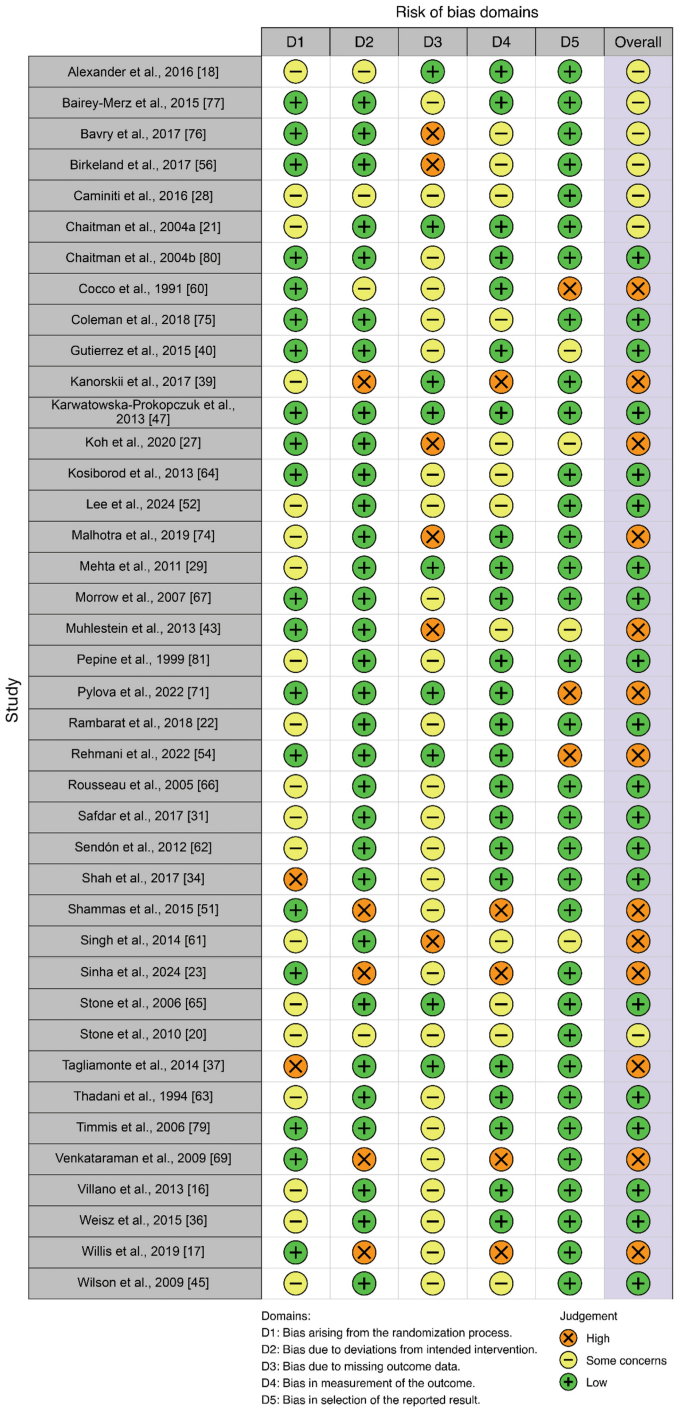



**FIGURE 2: RoB 2 for the risk of bias assessment of RCTs**

RoB 2, Risk of Bias 2; RCTs, randomized controlled trials

Non-randomized studies: Risk of bias was assessed using the ROBINS-I tool across seven domains (Figure *3*). The most frequent concerns were related to confounding and classification of interventions, with nearly all studies rated as being at critical risk, reflecting the inherent limitations of observational designs and the lack of adequate adjustment for potential confounders. Deviations from intended interventions and outcome measurement also frequently showed moderate-to-critical risk, particularly in studies lacking blinding or standardized assessment methods. By contrast, participant selection and selective reporting were more often judged to be at low risk, suggesting that these issues were less problematic. Missing outcome data varied across studies, with some judged at low risk but others at moderate risk due to incomplete follow-up.

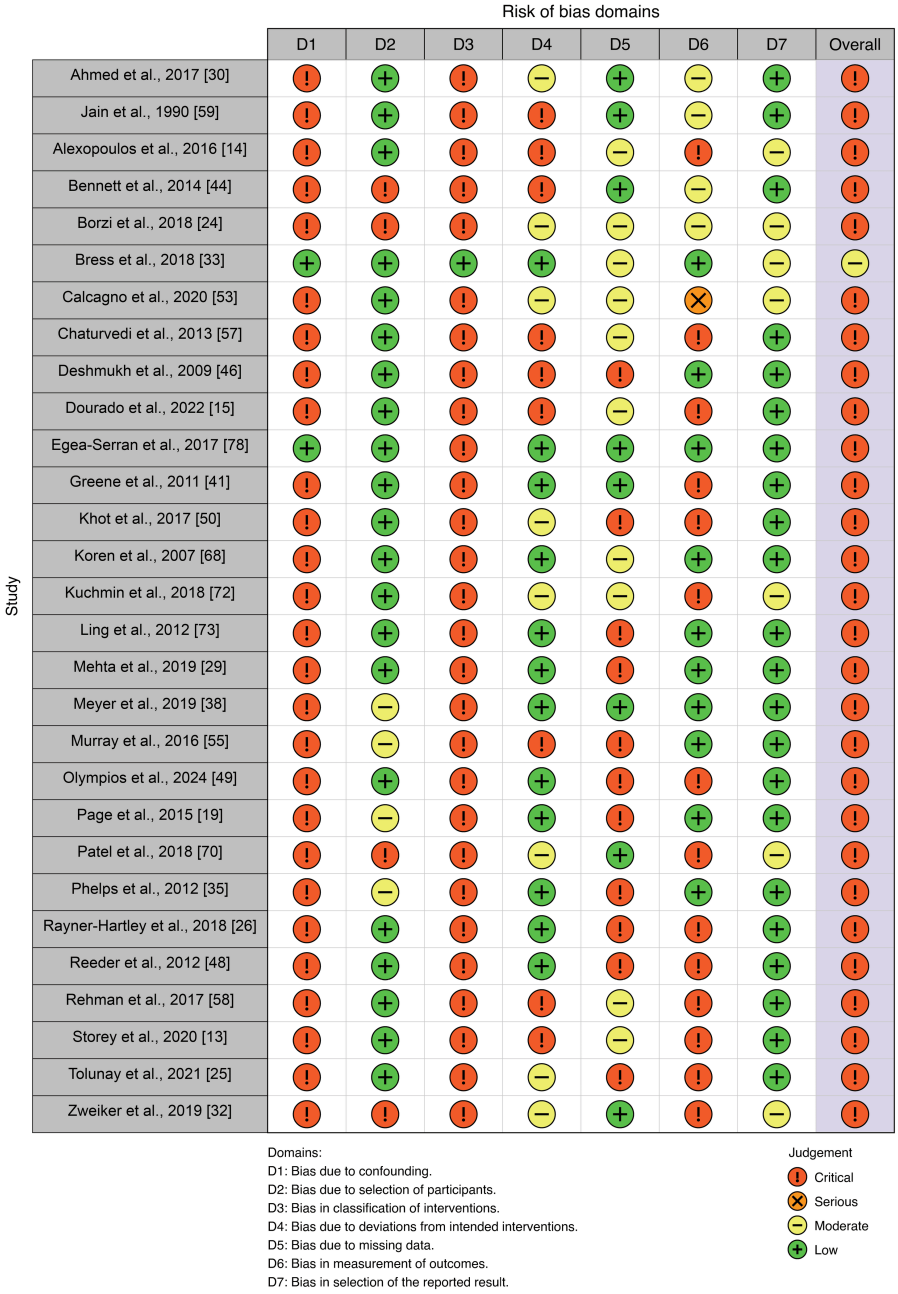



**FIGURE 3: ROBINS-I risk of bias assessment of non-RCTs**

RCTs: randomized controlled trials

*SAQ Domains*

The analysis showed statistically significant improvements in both the angina frequency and angina stability domains (Table 2).

| | Overall | | >6 months | | Microvascular disease | | Obstructive disease | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI |
| Seattle Angina Questionnaire: domains | | | | | | | | |
| Angina frequency | 9 | 4.63 (1.06-8.21) | 2 | 1.08 (-1.08-3.23) | 4 | 7.89 (0.94-14.84) | 5 | 2.23 (-0.14-4.60) |
| Angina stability | 7 | 12.00 (1.65-22.36) | 1 | NA | 4 | 20.35 (9.92-30.78) | 3 | 0.22 (-2.31-2.74) |
| Physical limitation | 7 | 2.94 (-4.05-9.92) | 1 | NA | 4 | 6.29 (2.59-9.99) | 3 | -4.14 (-18.94-10.66) |
| QoL | 7 | 6.16 (-0.46-12.77) | 1 | NA | 4 | 10.85 (2.80-18.91) | 3 | -0.18 (-2.13-1.77) |
| Treatment satisfaction | 7 | 0.01 (-5.22-5.25) | 1 | NA | 4 | 1.05 (-8.45-10.56) | 3 | -0.32 (-1.68-1.05) |
| Exercise parameters | | | | | | | | |
| Exercise duration | 11 | 33.15 (27.39-38.92) | 3 | 31.40 (26.59-36.22) | 2 | 39.98 (-22.17-102.13) | 9 | 33.10 (27.27-38.94) |
| Time to angina | 9 | 42.87 (34.23-51.51) | 3 | 48.91 (44.40-53.43) | NA | NA | 9 | 42.87 (34.23-51.51) |
| Time to 1-mm ST depression | 10 | 43.23 (33.81-52.65) | 3 | 45.94 (40.39-51.49) | 1 | NA | 9 | 42.58 (33.10-52.05) |

**TABLE 2: Primary meta-analysis of Seattle Angina Questionnaire domains and exercise parameters**

CI, confidence interval; QoL, quality of life; NA, not available

Based on nine studies, there was a mean improvement of 4.63 points (95% CI: 1.06-8.21) in the angina frequency domain and 12.00 points (95% CI: 1.65-22.36) in the angina stability domain. No statistically significant effects were observed for physical limitation (MD, 2.94; 95% CI, -4.05-9.92), QoL (MD, 6.16; 95% CI, -0.46-12.77), or treatment satisfaction (MD, 0.01; 95% CI, -5.22-5.25) domains (Figure *4a*-*4e*).

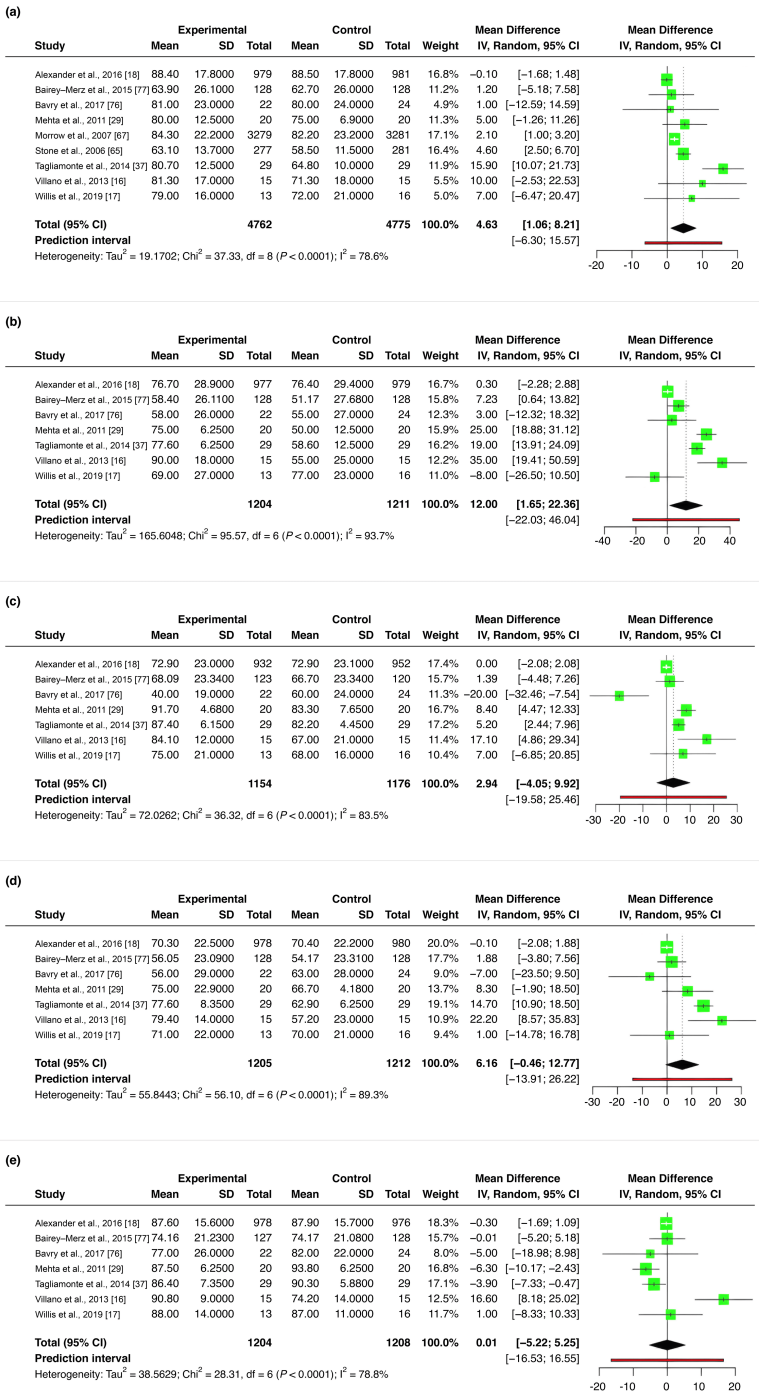



**FIGURE 4: Forest plot of the effect of ranolazine on (a) SAQ angina frequency, (b) SAQ angina stability, (c) SAQ physical limitation, (d) SAQ quality of life, and (e) SAQ treatment satisfaction**

SAQ, Seattle Angina Questionnaire; SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance

When subgroup analysis was performed on studies with a follow-up of >6 months, the improvement in angina frequency was no longer statistically significant (MD, 1.08; 95% CI, -1.08-3.23). There was insufficient data to produce pooled estimates for the other SAQ domains in this subgroup. In the subgroup analysis of patients with microvascular disease, the benefits were more pronounced and widespread. Statistically significant improvements were seen not only in angina frequency (MD, 7.89; 95% CI, 0.94-14.84) and angina stability (MD, 20.35; 95% CI, 9.92-30.78) but also in physical limitation (MD, 6.29; 95% CI, 2.59-9.99) and QoL (MD, 10.85; 95% CI, 2.80-18.91); treatment satisfaction did not show a significant

improvement in this subgroup (MD, 1.05; 95% CI, -8.45-10.56) (Figure *5a*-*5e*).

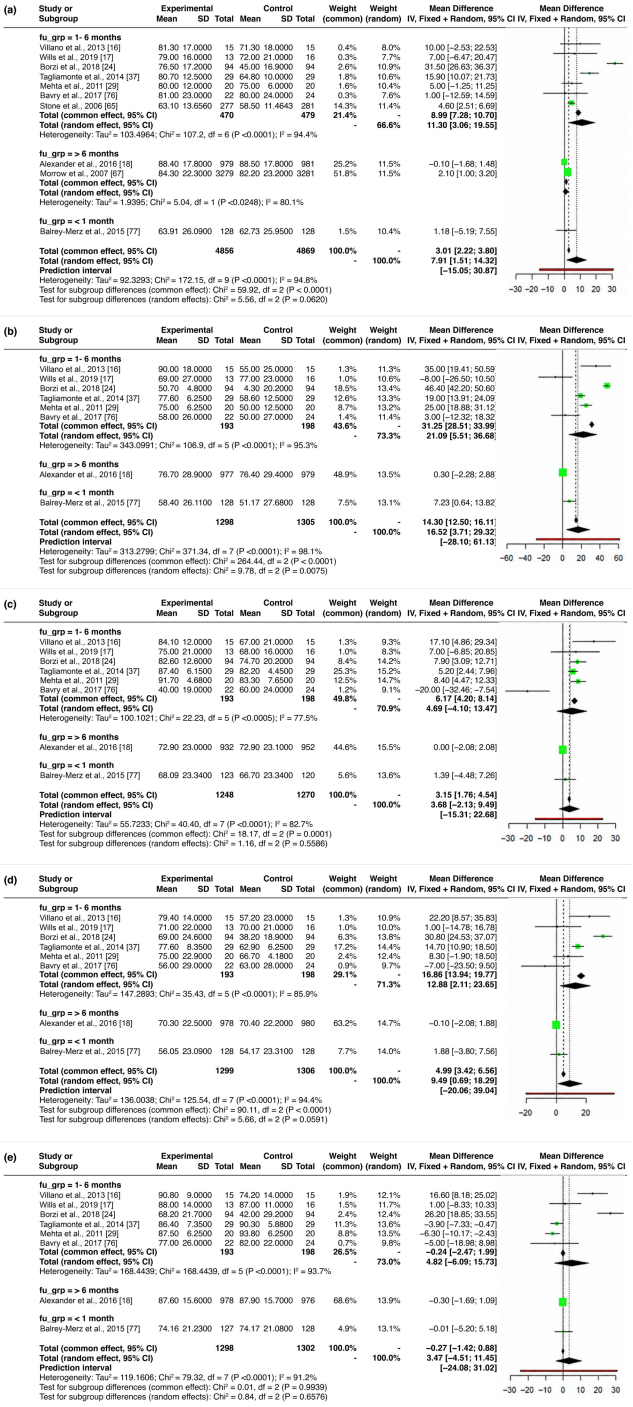



**FIGURE 5: Forest plot of the effect of ranolazine based on follow-up duration on (a) SAQ angina frequency, (b) SAQ angina stability, (c) SAQ physical limitation, (d) SAQ quality of life, and (e) SAQ treatment satisfaction**

SAQ, Seattle Angina Questionnaire; SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance

Conversely, in the subgroup of patients with obstructive disease, no statistically significant improvements were found across any of the five SAQ domains.

*Exercise Parameters*

The overall analysis demonstrated significant improvements in objective exercise capacity. Pooled data from 11 studies showed increases in exercise duration (MD, 33.15 seconds; 95% CI, 27.39-38.92), time to angina onset (MD, 42.87 seconds; 95% CI, 34.23-51.51), and time to 1-mm ST depression (MD, 43.23 seconds; 95% CI, 33.81-52.65). These benefits were maintained in studies with >6 months of follow-up and in the obstructive disease subgroup. However, in the microvascular disease subgroup, the improvement in exercise duration was not statistically significant (MD, 39.98 seconds; 95% CI, -22.17-102.13), with no pooled data available for other exercise parameters.

*Major Adverse Cardiac Events and Adverse Events*

The overall analysis found a statistically significant reduction in the risk of any MACE (pooled estimate: RR, 0.89; 95% CI, 0.84-0.94), CABG (RR, 0.55; 95% CI, 0.35-0.86), any revascularization such as PCI or CABG (RR, 0.77; 95% CI, 0.64-0.91), MI (RR, 0.91; 95% CI, 0.84-0.98), and hospitalization (RR, 0.87; 95% CI, 0.77-0.98) (Table *3*).

| | **Overall** | | **>6 months** | | **Microvascular disease** | | **Obstructive disease** | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI |
| MACE | | | | | | | | |
| Any MACE | 5 | 0.89 (0.84-0.94) | 5 | 0.89 (0.84-0.94) | NA | NA | 5 | 0.89 (0.84-0.94) |
| PCI | 3 | 0.80 (0.55-1.18) | 2 | 0.98 (0.71-1.36) | NA | NA | 1 | NA |
| CABG | 3 | 0.55 (0.35-0.86) | 2 | 1.05 (0.18-6.25) | NA | NA | 1 | NA |
| Any revascularization | 7 | 0.77 (0.64-0.91) | 6 | 0.83 (0.75-0.93) | NA | NA | 5 | 0.83 (0.68-1.00) |
| MI | 8 | 0.91 (0.84-0.98) | 6 | 0.91 (0.84-0.98) | 1 | NA | 7 | 0.94 (0.84-1.06) |
| Hospitalization | 5 | 0.87 (0.77-0.98) | 4 | 0.88 (0.75-1.03) | 1 | NA | 4 | 0.88 (0.75-1.03) |
| Cardiac death | 5 | 1.02 (0.86-1.20) | 5 | 1.02 (0.86-1.20) | NA | NA | 5 | 1.02 (0.86-1.20) |
| All mortality | 4 | 1.00 (0.86-1.16) | 3 | 1.00 (0.86-1.16) | NA | NA | 4 | 1.00 (0.86-1.16) |
| Adverse events | 11 | 1.45 (1.27-1.66) | 3 | 1.58 (1.27-1.97) | NA | NA | 11 | 1.45 (1.27-1.66) |

**TABLE 3: Primary meta-analysis of cardiovascular outcomes**

CI, confidence interval; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

There was no significant effect on PCI, cardiac death, or all-cause mortality. However, the risk of adverse events significantly increased (RR, 1.45; 95% CI, 1.27-1.66).

In the >6-month follow-up subgroup, the significant risk reductions for any MACE (RR, 0.89; 95% CI, 0.84-0.94), any revascularization such as PCI or CABG (RR, 0.83; 95% CI, 0.75-0.93), and MI (RR, 0.91; 95% CI, 0.85-0.99) were maintained. However, the benefits of CABG and hospitalization were no longer statistically significant in this longer-term follow-up. The increased risk of adverse events remained significant (RR, 1.58; 95% CI, 1.27-1.97). No data were available on MACE or adverse CABG events in the microvascular disease subgroup. In the obstructive disease subgroup, the only MACE outcome that remained statistically significant was the reduction in any MACE (RR, 0.89; 95% CI, 0.84-0.94). The risk reductions for any

revascularization, such as PCI or CABG, MI, and hospitalization, were no longer statistically significant in this subgroup. The increased risk of adverse events remained significant and was identical to the overall analysis (RR, 1.45; 95% CI, 1.27-1.66).

*Sensitivity Analysis: Results Excluding High-Risk Studies*

A sensitivity analysis was performed, excluding high-risk studies, to evaluate the robustness of the primary findings.

SAQ domains: After excluding high-risk studies, the improvement in angina frequency remained statistically significant but was attenuated (2.48; 95% CI, 0.39-4.56). Angina's stability also remained significant (15.85; 95% CI, 0.71-30.98) (Table *2*).

Exercise parameters: The improvements in exercise capacity were highly robust. Significant gains were maintained for exercise duration (32.08 seconds; 95% CI, 26.84-37.32), time to angina onset (42.87 seconds; 95% CI, 34.23-51.51), and time to 1-mm ST depression (43.23 seconds; 95% CI, 33.81-52.65). The results for time to angina onset and time to 1-mm ST depression were identical to the primary analysis. In contrast, for exercise duration, only one study was excluded due to a high risk of bias (Table *4*).

| | Overall | | >6 months | | Microvascular disease | | Obstructive disease | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI |
| Seattle Angina Questionnaire: domains | | | | | | | | |
| Angina frequency | 6 | 2.48 (0.39-4.56) | 2 | 1.08 (-1.08-3.23) | 3 | 3.91 (-0.30-8.12) | 3 | 2.12 (-0.43-4.68) |
| Angina stability | 4 | 15.85 (0.71-30.98) | 1 | NA | 3 | 21.39 (5.79-36.98) | 1 | NA |
| Physical limitation | 4 | 5.25 (-0.99-11.48) | 1 | NA | 3 | 7.64 (0.16-15.11) | 1 | NA |
| QoL | 4 | 6.25 (-2.22-14.72) | 1 | NA | 3 | 9.45 (-1.69-20.60) | 1 | NA |
| Treatment satisfaction | 4 | 1.93 (-7.00-10.86) | 1 | NA | 3 | 2.99 (-10.07-16.05) | 1 | NA |
| Exercise parameters | | | | | | | | |
| Exercise duration | 9 | 32.08 (26.84-37.32) | 3 | 31.40 (26.59-36.22) | 1 | NA | 8 | 32.03 (26.76-37.29) |
| Time to angina | 9 | 42.87 (34.23-51.51) | 3 | 48.91 (44.40-53.43) | NA | NA | 9 | 42.87 (34.23-51.51) |
| Time to 1-mm ST depression | 10 | 43.23 (33.81-52.65) | 3 | 45.94 (40.39-51.49) | 1 | NA | 9 | 42.58 (33.10-52.05) |

**TABLE 4: Sensitivity analysis excluding studies with high risk of bias: clinical endpoints**

CI, confidence interval; QoL, quality of life

MACE and adverse events: The sensitivity analysis confirmed the risk reductions for any MACE (0.89; 95% CI, 0.84-0.95) and MI (0.91; 95% CI, 0.84-0.98) (Table *5*).

| | Overall | | >6 months | | INOCA | | Obstructive disease | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI | Number of studies | Pooled estimate with CI |
| MACE | | | | | | | | |
| Any MACE | 4 | 0.89 (0.84-0.95) | 4 | 0.89 (0.84-0.95) | NA | NA | 4 | 0.89 (0.84-0.95) |
| PCI | 1 | NA | NA | NA | NA | NA | Nil | NA |
| CABG | 1 | NA | NA | NA | NA | NA | Nil | NA |
| Any Revascularization | 4 | 0.82 (0.67-1.02) | 4 | 0.82 (0.67-1.02) | NA | NA | 4 | 0.82 (0.67-1.02) |
| MI | 7 | 0.91 (0.84-0.98) | 5 | 0.91 (0.84-0.99) | 1 | NA | 6 | 0.95 (0.85-1.07) |
| Hospitalization | 4 | 0.88 (0.75-1.03) | 4 | 0.88 (0.75-1.03) | NA | NA | 4 | 0.88 (0.75-1.03) |
| Cardiac death | 4 | 1.02 (0.86-1.20) | 4 | 1.02 (0.86-1.20) | NA | NA | 4 | 1.02 (0.86-1.20) |
| All mortality | 4 | 1.00 (0.86-1.16) | 3 | 1.00 (0.86-1.16) | NA | NA | 4 | 1.00 (0.86-1.16) |
| Adverse events | 10 | 1.45 (1.25-1.67) | 2 | 1.59 (1.17-2.17) | NA | NA | 10 | 1.45 (1.25-1.67) |

**TABLE 5: Sensitivity analysis excluding studies with high risk of bias: clinical endpoints and adverse events**

CI, confidence interval; INOCA, ischemia with non-obstructive coronary arteries; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

The increased risk of adverse events also remained almost similar and significant (1.45; 95% CI, 1.25-1.67). The risk reductions for MACE and MI were robust, with point estimates identical to those in the primary analysis despite the exclusion of one study assessed as high risk of bias. However, the protective effects on any revascularization PCI or CABG (0.82; 95% CI, 0.67-1.02) and hospitalization (0.88; 95% CI, 0.75-1.03) were no longer statistically significant, indicating that the high-risk studies drove these benefits in the primary analysis. The increased risk of adverse events was also confirmed to be a consistent finding.

*Grading of Evidence*

The pooled outcomes across clinical domains are summarized in Table *3*. The GRADE certainty of evidence summary is given in Table *6*.

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty |
|---|---|---|---|---|---|---|
| | | | SoC | Ranolazine | Difference | |
| Overall MACE | 13795 (five RCTs) | RR = 0.89 (0.84-0.94) | 259 per 1000 | 231 per 1000 (218-243) | 28 fewer per 1000 (from 41 fewer to 16 fewer) | □□□□ High |
| PCI | 41164 (three non-randomized studies) | RR = 0.80 (0.55-1.18) | 178 per 1000 | 142 per 1000 (98-210) | 36 fewer per 1000 (from 80 fewer to 32 more) | □◯◯◯ Very low |
| CABG | 41164 (three non-randomized studies) | RR = 0.55 (0.35-0.86) | 46 per 1000 | 25 per 1000 (16-39) | 21 fewer per 1000 (from 30 fewer to 6 fewer) | □◯◯◯ Very low |
| Any revascularization | 126120 (seven non-randomized studies) | RR = 0.77 (0.64-0.91) | 175 per 1000 | 134 per 1000 (112-159) | 40 fewer per 1000 (from 63 fewer to 16 fewer) | □◯◯◯ Very low |
| Hospitalization | 17255 (five RCTs) | RR = 0.87 (0.77-0.98) | 273 per 1000 | 238 per 1000 (211-268) | 36 fewer per 1000 (from 63 fewer to 5 fewer) | □□◯◯ Low |
| Myocardial infarction | 50800 (eight RCTs) | RR = 0.91 (0.84-0.98) | 90 per 1000 | 82 per 1000 (75-88) | 8 fewer per 1000 (from 14 fewer to 2 fewer) | □□□□ High |
| Cardiac death | 12834 (five RCTs) | RR = 1.02 (0.81-1.29) | 43 per 1000 | 43 per 1000 (34-55) | 1 more per 1000 (from 8 fewer to 12 more) | □□□□ High |
| All-cause mortality | 13664 (four RCTs) | RR = 1.00 (0.86-1.16) | 48 per 1000 | 48 per 1000 (41-56) | 0 fewer per 1000 (from 7 fewer to 8 more) | □□□□ High |
| Adverse events | 12534 (11 RCTs) | RR = 1.45 (1.27-1.66) | 113 per 1000 | 164 per 1000 (144-188) | 51 more per 1000 (from 31 more to 75 more) | □□□◯ Moderate |

**TABLE 6: Summary of findings for ranolazine versus SoC for chronic stable angina**

CI, confidence interval; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; RCTs, randomized controlled trials; RR, risk ratio; SoC, standard of care

Ranolazine was associated with a high-certainty reduction in overall MACE and MI while showing no difference in cardiac death or all-cause mortality, also supported by high-certainty evidence. For hospitalization, the evidence suggested a reduction, but the certainty was low. For PCI, CABG, and any revascularization PCI or CABG, findings indicated possible reductions; however, the certainty of evidence was very low, largely due to reliance on non-randomized data. Ranolazine was consistently associated with an increased risk of adverse events, with the certainty of this evidence rated as moderate.

The summary of findings for ranolazine versus standard of care (SoC) for improving SAQ with GRADE is given in Table *7*.

| Outcome | Patients (studies), N | Relative effect (95% CI) | Certainty |
|---|---|---|---|
| SAQ angina frequency | 9537 (nine RCTs) | 4.63 (1.06-8.21) | □□◯◯ Low |
| SAQ angina stability | 2415 (seven RCTs) | 12 (1.65-22.36) | □◯◯◯ Very low |
| SAQ physical limitation | 2330 (seven RCTs) | 2.94 (-4.05-9.92) | □◯◯◯ Very low |
| SAQ quality of life | 2417 (seven RCTs) | 6.16 (-0.46-12.77) | □◯◯◯ Very low |
| SAQ treatment satisfaction | 2412 (seven RCTs) | 0.01 (-5.22-5.25) | □◯◯◯ Very low |

**TABLE 7: Summary of findings for ranolazine versus SoC for improving SAQ**

CI, confidence interval; SAQ, Seattle Angina Questionnaire; SoC, standard of care; RCTs, randomized controlled trials

Evidence from RCTs showed that ranolazine was associated with a modest improvement in SAQ angina frequency, supported by low-certainty evidence. For SAQ stability, the results suggested a possible benefit,

but the certainty was rated as very low. For SAQ physical limitation, QoL, and treatment satisfaction, findings did not demonstrate a significant benefit, and the certainty of evidence was very low across all domains.

The evidence for ranolazine improving exercise parameters in patients with CSA is rated as high certainty (Table *8*).

| Outcome | Patients (studies), N | Relative effect (95% CI) | Certainty |
|---|---|---|---|
| Exercise duration | 4853 (11 RCTs) | 33.15 (27.39-38.92) | □□□□ High |
| Time to angina | 4751 (nine RCTs) | 42.87 (34.23-51.51) | □□□□ High |
| Time to 1-mm ST depression | 4772 (10 RCTs) | 43.23 (33.81-52.65) | □□□□ High |

**TABLE 8: Summary of findings for ranolazine versus SoC for improving exercise parameters**

CI, confidence interval; RCTs, randomized controlled trials; SoC, standard of care

This indicates strong confidence that ranolazine increases exercise duration, delays time to angina onset, and prolongs time to 1-mm ST depression compared with SoC.

## Discussion

This systematic review and meta-analysis of 69 studies evaluates the efficacy, safety, and clinical role of ranolazine in CSA management. Importantly, our findings extend beyond prior reviews by demonstrating that ranolazine is associated with a statistically significant reduction in MACE and MI, suggesting a broader cardioprotective effect. We also observed substantial improvement in QoL domains, particularly in patients with microvascular disease, underscoring its targeted benefit in this subgroup. Ranolazine was further associated with reductions in some revascularization outcomes, such as PCI or CABG in pooled analyses, whereas no change was observed in cardiac death or all-cause mortality.

Patient-reported QoL outcomes mirrored functional gains. Ranolazine produced statistically significant and likely clinically relevant improvements in SAQ angina frequency, angina stability, and QoL domains, with the most pronounced effects observed in the overall pooled analysis and microvascular subgroup analysis. These symptomatic benefits are important because the relief of angina and improvement in QoL are primary treatment goals in CSA management. The treatment satisfaction and physical limitation domains showed more minor, nonsignificant pooled changes, suggesting that while patients experienced fewer and more stable angina episodes, the translation to broader physical function and treatment satisfaction may be more variable and influenced by comorbidities, baseline functional status, or expectations [2,82].

The robust and statistically significant improvements in total exercise duration (MD: 33.15 seconds), time to angina onset (MD: 42.87 seconds), and time to 1-mm ST depression (MD: 43.23 seconds) highlight the impact of ranolazine's established efficacy. These exercise benefits were sustained across subgroup analyses for longer follow-ups (>6 months) and in patients with obstructive disease, as well as sensitivity analyses excluding studies at high risk of bias. Taken together, these findings suggest a durable anti-ischemic effect that is physiologically plausible given ranolazine's inhibition of late inward sodium current and the consequent reduction of intracellular calcium and myocardial diastolic tension.

These results demonstrate remarkable consistency with prior high-quality meta-analyses. A 2023 review by Manolis et al. reported nearly identical improvements of 30 seconds in exercise duration, 40 seconds in time to angina, and 44 seconds in time to ST depression [83]. An earlier review by Savarese et al. (2013) also found a weighted MD of 31.9 seconds for exercise duration, further reinforcing this effect size [84]. A meta-analysis by Banon et al. (2014), which included eight RCTs, also demonstrated significant increases in total exercise duration (23.9 seconds) and reductions in weekly angina attacks [5]. Our results, drawn from a much larger pool of 69 studies, reinforce these foundational efficacy findings. More comprehensively, the Cochrane review, encompassing 17 RCTs, similarly concluded that ranolazine probably reduces angina attack frequency and slightly improves exercise tolerance, supporting its role as symptomatic therapy [85]. Where our analysis adds significant value is in the detailed synthesis of patient-reported outcomes, showing clinically meaningful improvements across multiple SAQ domains, a level of detail not fully captured in earlier reviews that focused primarily on functional parameters.

On MACE-related outcomes, pooled results were mixed. The observed reduction in overall MACE (RR: ~0.89), as well as reductions in CABG and any revascularization, such as PCI or CABG, is intriguing but should be interpreted cautiously. The apparent reduction in downstream revascularization, such as PCI or CABG, may

partly reflect symptomatic improvement (fewer ischemic episodes prompting invasive evaluation) rather than a disease-modifying effect on atherosclerotic progression. Our observation of the impact of ranolazine on all-cause or cardiac mortality aligns with previous syntheses, indicating that ranolazine is as safe as other antianginal agents, with its primary benefit centered on symptomatic relief rather than mortality reduction. While prior meta-analysis of RCTs found no significant effect of ranolazine on mortality or MI, our analysis identified a small potential reduction in MI and downstream revascularization, such as PCI or CABG [14]. This divergence is likely attributable to the distinct composition of our evidence base; prior meta-analyses were primarily restricted to RCTs, whereas our analysis incorporated a broader evidence base, including large-scale observational and real-world database studies. These additional data may have provided the statistical power to detect signals not apparent in smaller, selected trial populations. Nonetheless, this finding should be considered hypothesis-generating, as it may reflect symptomatic improvement leading to fewer invasive procedures rather than an actual disease-modifying effect, a caution echoed in our primary analysis.

Safety analyses showed a higher risk of adverse events (RR: ~1.45), consistent follow-up durations, disease subgroups, and sensitivity analyses. Events were non-fatal and included gastrointestinal symptoms, dizziness, constipation, and occasional dose-limiting effects or heart rate corrected QT (QTc) interval prolongation, aligning with prior meta-analytic findings. This finding is consistent with the safety signals reported in major prior meta-analyses on the topic [85]. Substantial heterogeneity across several outcomes, especially SAQ domains and angina frequency, likely reflects differences in study populations, dosing, background therapy, outcome definitions, follow-up duration, and study design. Follow-up-based subgroup analyses explained some variability: symptom and QoL benefits were clear overall and in microvascular disease but not in studies with more than six months of follow-up, possibly due to attrition, dose changes, or more refractory patient cohorts.

*Patients With Microvascular Disease*

As underscored by the SAQ subgroup analysis, the benefits of ranolazine appear particularly pronounced in patients with microvascular disease. This strong clinical signal is supported by a growing body of mechanistic evidence demonstrating that ranolazine can improve objective physiological measures of microvascular function. Multiple systematic reviews have converged on this point. Ling et al. (2024) conducted a meta-analysis of eight RCTs and found that ranolazine significantly increased CFR with a standardized MD of 1.16 and also improved the myocardial perfusion reserve index [86]. An earlier review by Kofler et al. (2021) similarly concluded that ranolazine may be associated with improvements in CFR in this population [87].

While some individual trials, such as the MARINA trial [27] and a placebo-controlled trial by Bairey Merz et al. [77], did not show an overall benefit on their primary endpoints of change in CFR, both trials reported important subgroup findings. In these studies, patients with more severe baseline microvascular dysfunction (e.g., CFR < 2.0 or 2.5) did appear to derive a significant benefit from ranolazine, suggesting a targeted effect in those with the most advanced pathology. Collectively, this evidence positions ranolazine as a leading therapeutic option for the challenging microvascular disease population.

*Patients With Type 2 Diabetes: A Unique Dual-Benefit Agent*

Although not a primary endpoint of this meta-analysis, evidence strongly supports a meaningful role for ranolazine in patients with diabetes. The TERISA trial showed clear reductions in weekly angina despite background antianginal therapy [64]. Beyond symptom relief, ranolazine provides a metabolic benefit: a meta-analysis of over 4400 patients, a mean glycosylated hemoglobin (HbA1c) reduction of about 0.5%, consistent with findings from CARISA [27]. This combined antianginal and antihyperglycemic effect makes ranolazine an attractive option for patients with type 2 diabetes and CSA who remain symptomatic or cannot tolerate therapies that affect heart rate or blood pressure [88]. Clinicians should counsel patients about common, non-serious adverse effects and consider ECG monitoring for patients at risk of QT prolongation. Ranolazine does not reduce mortality and should not replace guideline-directed therapies known to improve prognosis.

Future research should evaluate hard clinical outcomes, such as MI, hospitalization, and revascularization, such as PCI or CABG, in well-defined groups, including those with refractory post-PCI angina, microvascular angina, and diabetes. In accordance with recent comparative evaluations of antianginal regimens, the role of metabolic modulators as add-on therapy has gained significant clinical interest. While ranolazine improves exercise duration and reduces anginal frequency through partial fatty acid oxidation inhibition, similar metabolic agents such as trimetazidine offer comparable anti-ischemic benefits via distinct yet complementary mechanisms. Integrating these comparative perspectives into the management of refractory angina provides a broader framework for optimizing individualized antianginal therapy [15]. The standardized reporting of patient-centered outcomes, especially consistent SAQ use with predefined clinically important differences, is needed to strengthen evidence synthesis. Long-term safety data, including arrhythmia risk and drug interactions, remain essential.

*Strengths and Limitations of the Current Review*

The primary strength of this review lies in its comprehensive scope, which incorporates many studies and evaluates a broad range of clinical and patient-reported outcomes. The rigorous methodology, including adherence to PRISMA 2020 reporting standards, prospective protocol registration with PROSPERO, and the use of robust statistical methods, enhances its validity. The detailed subgroup and sensitivity analyses provide crucial insights into the heterogeneity of treatment effects across different patient populations and help to establish the robustness of the primary findings.

The main limitations are the reliance on non-randomized studies for MACE and revascularization, which introduces confounding risks, and significant heterogeneity in SAQ domains. Additionally, the MACE reduction is a post hoc, hypothesis-generating finding from underpowered trials, while the inclusion of small, single-center studies may have influenced pooled estimates. Furthermore, while subgroup analyses based on specific clinical presentations such as microvascular angina would be of considerable interest, the current literature is limited by a scarcity of primary trials explicitly isolating these cohorts and insufficient patient-level data. Consequently, future clinical trials and individual participant data meta-analyses are necessary to evaluate the therapeutic efficacy of ranolazine in these subsets of patients.

## Conclusions

In this systematic review and meta-analysis, ranolazine was associated with meaningful improvements in angina-related symptoms, exercise tolerance, and patient-reported QoL among patients with CSA, with particularly notable benefits in those with microvascular disease. The findings also suggest potential reductions in MI, MACE, and downstream revascularization; however, these outcome signals should be interpreted cautiously because they were influenced by heterogeneity and the inclusion of non-randomized evidence. Importantly, ranolazine did not demonstrate a mortality benefit, reinforcing its role primarily as an antianginal and QoL-enhancing therapy rather than a prognostic intervention.

Overall, ranolazine may be considered a useful adjunctive treatment for patients who remain symptomatic despite standard antianginal therapy, especially when heart rate or blood pressure limitations restrict the use of other agents. Clinicians should balance its symptomatic benefits against the increased risk of generally non-fatal adverse events and consider appropriate monitoring in patients at risk for QT prolongation. Future adequately powered, long-term randomized trials are warranted to clarify its effects on hard cardiovascular outcomes, define the patient subgroups most likely to benefit, and standardize patient-centered outcome reporting.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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