Efficacy and safety of Rhodiola crenulata injection in the treatment of acute coronary syndrome: A meta-analysis with machine learning

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Systematic Review

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Posted Date: June 22nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9987430/v2

Additional Declarations: The authors declare no competing interests.

Efficacy and safety of *Rhodiola crenulata* injection in the treatment of acute coronary syndrome: A meta-analysis with machine learning

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Abstract

Background: Acute coronary syndrome (ACS) remains a leading cause of cardiovascular death and disability. Despite increasingly comprehensive guideline-directed therapy and the widespread use of contemporary revascularization, substantial unmet clinical needs persist. In China, Rhodiola crenulata injection (RCI) is widely used as an adjunct to standard Western medicine (WM) for ACS, yet its benefit-risk profile remains uncertain.

Methods: RCTs up to July 2025 were retrieved from eight databases. ACS patients receiving RCI + WM or WM alone were included. Meta-analyses were performed using RevMan 5.4 and Stata 17.0, with TSA applied to evaluate information size and robustness. Risk of bias and evidence certainty were assessed using RoB 2 and GRADE, respectively. Five machine learning models (Random Forest, XGBoost, Lasso, Multilayer Perceptron, and a stacking model) were used to model time–effect relationships and optimal RCI treatment durations.

Results: Forty-five RCTs (n = 4,217) were included. Compared to WM alone, RCI + WM resulted in a reduced incidence of MACE, angina attacks, duration of angina attacks, TC and LDL-C levels, improved total clinical efficacy, electrocardiographic efficacy and HDL-C levels. The incidence of adverse events was not statistically different. Machine learning predicted the optimal treatment durations of RCI as 10.08 days for UA and 14.39 days for AMI.

Conclusion: In ACS, adding RCI as an adjunct to WM demonstrates efficacy in reducing MACE, improving clinical symptoms, myocardial ischemia, and lipid profiles, thereby providing additional clinical benefits.

Keywords: *Rhodiola crenulata* injection, acute coronary syndrome, systematic review, meta-analysis, randomized controlled trials, machine learning

1 Introduction

Acute coronary syndrome (ACS) encompasses clinical conditions resulting from an abrupt decrease or halt in myocardial blood flow, causing ischemia or infarction (Pouralijan Amiri et al., 2019). It encompasses unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (H. Wang et al., 2020). Despite substantial progress, including advances in interventional therapy, ACS remains a critical global health burden due to high morbidity and mortality (Bergmark et al., 2022). In the Asia-Pacific, ACS is responsible for about half of heart disease fatalities (Yan et al., 2018). Dyslipidemia, a modifiable determinant, is a risk factor for both the onset and progression of ACS, significantly contributing to its pathogenesis through elevated low-density lipoprotein cholesterol (LDL-C) (Yadav and Sawhney, 2024).

ACS management focuses on restoring and maintaining coronary perfusion. Acute treatment relies on PCI, CABG, and thrombolysis, while secondary prevention uses pharmacological therapies (e.g., antiplatelets, lipid-lowering therapy, and rate/BP control) to reduce MACE risk (Sibbing et al., 2024). Despite advances such as surgery and stent implantation, MACE remains common and symptoms like cardiac pain often persist (Rao et al., 2025). These limitations highlighting the need for effective adjunctive strategies. In this context, Rhodiola crenulata has drawn increasing interest as an add-on to conventional therapy for potential symptom relief in ACS (Chen et al., 2022a).

Rhodiola crenulata is a plant species of the genus *Rhodiola* in the family *Crassulaceae*. It mainly grows in the Himalayan region, including Tibet, China, and Mongolia. Medicinally, it is derived from the dried root and rhizome of *R. crenulata* and has traditionally been used to enhance resistance to hypoxia (Zheng et al., 2011). As a traditional Chinese medicine, it widely used in the treatment of angina pectoris and hypoxia, and its injection has been used clinically for cardiovascular diseases, including coronary artery disease (Liang et al., 2024; Man et al., 2020). Moreover, numerous clinical trials of RCI in ACS have been published, providing preliminary evidence of its efficacy and safety.

However, few systematic reviews of RCI in ACS exist, and many were conducted earlier with notable methodological limitations. As a result, the evidence has not been fully translated into clinical decision-making, and the optimal treatment duration remains uncertain. To address these gaps, we integrated meta-analysis with machine learning to synthesize the available clinical data, with the aims of verifying the efficacy of RCI and estimating optimal treatment durations for ACS.

2 Materials and methods

This systematic review protocol was registered in PROSPERO (CRD420251046809) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA 2020) guidelines (Page et al., 2021).

2.1 Ethical statement

Ethics committee approval and written informed consent were not required for this study, as it included only previously published randomized clinical trials with prior ethics approval and informed consent.

2.2 Eligibility criteria

Inclusion criteria: 1) Study design: Randomized controlled trials were included. 2) Participants: Diagnosed with ACS (Rao et al., 2025). Supplementary A 1 provides comprehensive diagnostic criteria of ACS. Participants of any age, gender, race, and region were included. 3) Intervention and control: The control group received the standard western medicine (WM) for ACS, which included single/dual antiplatelet therapy, anticoagulation, anti-ischemic therapy, lipid-lowering therapy, renin-angiotensin-aldosterone system inhibition, and comprehensive management of blood pressure, glucose, and other risk factors. Supplemental oxygen, bed rest, and cardiac monitoring were provided as needed. RCI was given to the treatment group along with conventional treatment. Supplementary Material A2 contains comprehensive details about RCI (Table A.2) and the criteria for evaluating total clinical efficacy and electrocardiographic efficacy. 4) Outcomes: Primary outcomes: MACE, the frequency of angina attacks and the duration of angina attacks. Secondary outcomes: total clinical efficacy, electrocardiographic efficacy, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). Safety outcome: incidence of adverse events.

Exclusion criteria: 1) Studies containing inaccurate or incomplete data, or those where a sufficient amount of data could not be extracted. 2) Participants receiving other traditional Chinese treatments, such as acupuncture and other botanical drugs. 3) Only one of the duplicate studies were retained.

2.3 Information source and search strategy

The research in both Chinese and English originated from the China National Knowledge Infrastructure Database (CNKI), VIP Database for Chinese Technical Periodicals (VIP), Wanfang Database (Wanfang), Chinese Biomedical Literature Database (SinoMed), Web of Science, Pubmed, Embase, and Cochrane Library. Searches were conducted from the beginning of the databases to 10 July 2025. Combining subject terms with free-text terms was used for the search. The PubMed search strategy is detailed below (Table 1), with strategies for other databases available in Supplementary A 3.

2.4 Study screening and data extraction

The screening protocol comprised two stages. First, titles and abstracts were reviewed to pick out the trials that complied with the inclusion criteria. Second, in cases where more information was needed, the full text of the relevant trials was carefully examined. A standardized data extraction table was created, encompassing elements such as study title, primary author, publication year, source, sample size, participant age and gender, disease diagnosis and criteria, disease duration, treatment course, follow-up details, and study outcomes. For missing or unclear information, corresponding authors were contacted by email. If there was no response from the authors, the study was excluded from the current research. Two reviewers independently performed screening and data extraction; disagreements were resolved through discussion or a third reviewer.

2.5 Risk of bias assessment and evidence certainty

The risk of bias in the included RCTs was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019), two reviewers individually evaluated the potential for the risk of bias in each study. Differences were settled by engaging in discussions with the third reviewer. We used GRADE to rate certainty as high, moderate, low, or very low. The certainty of evidence for each outcome was evaluated independently by two reviewers, and a third reviewer was consulted to resolve differences (Balshem et al., 2011). Rules for assessment of risk of bias and evidence certainty are provided in Supplementary A 4.

2.6 Statistical analysis

The meta-analysis utilized Review Manager (Cochrane Collaboration, version 5.4) and Stata 17.0. Effect sizes for dichotomous variables were presented as relative risk (RR). For continuous outcomes, the meta-analysis used change values (post-minus-pre; mean ± SD) to calculate effect sizes, adopting mean difference (MD) as appropriate effect measures. The results of the statistical analysis were presented with 95% confidence intervals (CI). Statistical heterogeneity was evaluated using the *P* value and the I^2 statistic. $I^2 \leq 50\%$ indicated low heterogeneity; therefore, a fixed-effects model was applied. If significant heterogeneity was observed among the included trials, subgroup analysis or sensitivity analysis were conducted to identify potential sources. If the sources of heterogeneity remained undetermined, the random-effects model was employed. Funnel plots and Egger's test were used to assess publication bias in analysis involving data from more than 10 trials. An Egger's test P-value ≤ 0.05 was considered evidence of funnel-plot asymmetry, which may indicate potential publication bias.

2.7 Trial sequential analysis

Trial sequential analysis (software v0.9.5.10, two sided) was undertaken for the outcomes to determine whether the accumulated evidence was adequately powered and to limit random errors arising from repeated significance testing as new trials are added. The cumulative Z curve tracks the sequential build up of evidence against the conventional significance threshold, the TSA monitoring boundaries, and the required information size (RIS). A Z curve that exceeds the conventional boundary but does not cross the TSA boundary indicates that the nominally significant finding may still be vulnerable to random error and that additional trials may be needed. In contrast, crossing the TSA monitoring boundary supports a more robust conclusion. Attainment of the RIS further indicates that the information size requirement has been met (De Cassai et al., 2021).

2.8 Machine learning

2.8.1 Inclusion of study and data

We investigated the optimal treatment duration of RCI across the UA and AMI. After organizing and screening the original data, we included 38 studies covering nine outcome indicators: MACE, the frequency of angina attacks, the duration of angina attacks, total clinical efficacy, electrocardiographic efficacy, TC, TG, LDL-C and HDL-C.

2.8.2 Basic information of included articles

Treatment duration data for patients with UA and AMI were extracted study by study from each trial included in the meta-analysis. For each study, we identified and summarized the reported treatment-duration range, and then aggregated these ranges within each disease group.

2.8.3 Model interpretation

Machine learning outputs were visualized to display the results intuitively. The x-axis showed treatment duration, whereas the y-axis presented standardized outcome values. Because of standardization, the y-axis could include negative values when smaller raw values were transformed into negative standardized scores; importantly, this does not imply that the intervention at that duration aggravates the disease. Instead, negative values reflect a relatively smaller improvement in the outcome indicators attributable to the treatment. The scatter points corresponded to the observed outcome values, the colored curves illustrated the machine learning–predicted trajectories of outcomes across different treatment durations, and the light shading around each curve denoted the confidence intervals of the predictions. The optimal treatment duration was marked by the red dotted line.

3 Results

3.1 Study screening

The search retrieved 617 records. Following the elimination of 239 duplicates, 378 records were reviewed for title and abstract; 310 of these did not meet eligibility criteria. 68 reports proceeded to full-text evaluation, where 23 were excluded. A total of 45 RCTs were included in the analysis. The study screening process is illustrated in Figure 1.

3.2 Study characteristics

Table 2 presents a comprehensive summary of the characteristics of the trials included in this analysis. All 45 RCTs were conducted in China and published in Chinese between 2012 and 2023. These trials collectively involved 4,217 participants (2,122 individuals assigned to the intervention group and 2,095 to the control group). All RCTs compared RCI+WM with WM alone. The treatment regimen lasted between 7 and 60 days. Baseline characteristics were consistent across all trials.

3.3 Risk of bias assessment

The 45 trials were evaluated using the five domains of RoB 2. In 45 trials, issues were identified with the randomization process; 29 of these trials referenced randomization but failed to specify the implementation method. Additionally, all 45 trials failed to report allocation concealment. In 43 trials, concerns arose regarding deviations from the intended interventions, likely due to the absence of blinding. Two trials were deemed high risk due to potential significant impacts on results from deviations in intervention measures. Missing outcome data: all trials reported complete outcome data for randomized participants. Measurement of the outcome: 36 studies lacked blinding, which may have affected outcome measurement. Within the 36 trials, five trials were judged high risk because knowledge of the intervention could plausibly influence outcome measurement. Selection of the reported result: all trials faced issues with selective reporting of results because none had a preregistered protocol, and one trial was high risk for selective outcome reporting. In total, 39 trials

were assessed with some concerns, while 6 trials were deemed high risk. (Figure 2) presents the assessment of bias risk for the included trials.

3.4 Meta-analysis results

3.4.1 Primary outcomes

3.4.1.1 MACE

MACE was reported in 3 RCTs including 300 participants (Figure 3), demonstrating low heterogeneity (I^2 = 0%). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a fixed-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in reducing MACE [RR = 0.56, 95% CI (0.40, 0.78), p = 0.0007].

3.4.1.2 The frequency of angina attacks

The frequency of angina attacks was reported in 7 RCTs including 701 participants (Figure 4), with high heterogeneity among the studies (I^2 = 98%). Sensitivity analysis identified three influential studies. Excluding these studies maintained the direction and significance of the pooled effect and reduced heterogeneity (I^2 = 30%), suggesting their substantial contribution to heterogeneity. Therefore, a fixed-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in reducing the frequency of angina attacks [MD = -0.62, 95% CI (-0.89, -0.35), p < 0.00001].

3.4.1.3 The duration of angina attacks

The duration of angina attacks was reported in 6 RCTs including 578 participants (Figure 5), with substantial heterogeneity among the studies (I^2 = 89%). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a random-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in reducing the duration of angina attacks [MD = -1.76, 95% CI (-2.52, -1.00), p < 0.00001].

3.4.2 Secondary outcomes

3.4.2.1 Total clinical efficacy

Total clinical efficacy was reported in 27 RCTs including 2,507 participants (Figure 6), with low heterogeneity among the studies (I^2 = 22%). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a fixed-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM for total clinical efficacy [RR = 1.23, 95% CI (1.19, 1.28), p < 0.00001].

3.4.2.2 Electrocardiographic efficacy

Electrocardiographic efficacy was reported in 22 RCTs including 2,135 participants (Figure 7), with substantial heterogeneity among the studies (I^2 = 68%). Sensitivity analysis did not identify any study with a significant impact on the pooled

effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a random-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM for electrocardiographic efficacy [RR = 1.23, 95% CI (1.14, 1.34), $p < 0.00001$].

3.4.2.3 TC

TC was reported in 7 RCTs including 727 participants (Figure 8), with substantial heterogeneity among the studies ($I^2 = 76\%$). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a random-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in reducing TC levels [MD = -0.73, 95% CI (-1.00, -0.46), $p < 0.00001$].

3.4.2.4 TG

TG was reported in 6 RCTs including 591 participants (Figure 9), with substantial heterogeneity among the studies ($I^2 = 83\%$). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity, suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a random-effects model was employed to pool the results. The meta-analysis showed no statistically significant difference in reducing TG between RCI+WM and WM groups, suggesting that RCI+WM may be as effective as WM in reducing TG levels [MD = -0.16, 95% CI (-0.36, 0.03), $p = 0.10$].

3.4.2.5 HDL-C

HDL-C was reported in 6 RCTs including 633 participants (Figure 10), with high heterogeneity among the studies ($I^2 = 95\%$). Sensitivity analysis identified two influential studies. Excluding these studies did not change the direction or significance of the pooled effect, while heterogeneity decreased ($I^2 = 84\%$), suggesting their substantial contribution to heterogeneity. Due to persistent significant heterogeneity, a random-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in improving HDL-C levels [MD = 0.31, 95% CI (0.10, 0.52), $p = 0.003$].

3.4.2.6 LDL-C

LDL-C was reported in 9 RCTs including 968 participants (Figure 11), with high heterogeneity among the studies ($I^2 = 97\%$). Sensitivity analysis identified one influential study. Excluding this study did not change the direction or significance of the pooled effect, while heterogeneity decreased ($I^2 = 85\%$), suggesting their substantial contribution to heterogeneity. Due to persistent significant heterogeneity, a random-effects model was employed to pool the results. The meta-analysis showed that the effect estimate favored RCI+WM over WM in reducing LDL-C levels [MD = -0.35, 95% CI (-0.54, -0.17), $p = 0.0002$].

3.5 Adverse events

Adverse events were reported in 12 RCTs including 1,220 participants (Figure 12), with low heterogeneity among the studies ($I^2 = 0\%$). Sensitivity analysis did not identify any study with a significant impact on the pooled effect or heterogeneity,

suggesting that excluding any single study did not decrease the heterogeneity of the combined results. Therefore, a fixed-effects model was employed to pool the results. The meta-analysis showed no statistically significant difference in adverse events between RCI+WM and WM groups [RR = 1.37, 95% CI (0.74, 2.54), $p = 0.32$].

According to the results, only a few adverse events were observed during the treatment of ACS with RCI (Table 3). In the treatment group, 22 out of 613 participants (3.59%) reported adverse events; the main ones included nausea, headache, dizziness, inappetence, and mild gastrointestinal hemorrhage, etc. In the control group, 16 out of 607 participants (2.64%) experienced adverse events, primarily dizziness, headache, hemoptysis, and vascular pain. The incidence of adverse events was similar between the two groups.

3.6 Subgroup analysis and sensitivity analysis

Subgroup analyses were performed by treatment duration (Table 4). Compared with >10 days, the ≤10 days subgroup showed larger reductions in the frequency and duration of angina attacks and a greater decrease in LDL-C ($P < 0.05$). No significant subgroup differences were observed for the remaining outcomes ($P > 0.05$).

Another Subgroup analysis were performed by disease type (Table 5). The AMI subgroup showed a larger improvement in total clinical efficacy than the UA subgroup ($P = 0.03$). For TG, the subgroup difference was significant ($P = 0.0005$), with a significant reduction in the UA subgroup but no significant effect in the AMI subgroup. No statistically significant subgroup differences were observed for the other outcomes ($P > 0.05$).

For sensitivity analysis, heterogeneity decreased after excluding a small number of influential trials, while the pooled effects remained similar. These results support the robustness of our conclusions. For a comprehensive understanding, the detailed data related to the sensitivity analysis can be found in Supplementary A 5.

3.7 Publication bias

We examined funnel plots for electrocardiographic efficacy and total clinical efficacy. The funnel plot for electrocardiographic efficacy (Figure 13A) and total clinical efficacy (Figure 13B) were clearly asymmetric ($p < 0.0001$), suggesting that there may be publication bias.

3.8 Certainty of evidence

The certainty of evidence regarding the outcomes was evaluated with the GRADE methodology, as detailed in Table 6. The results demonstrated that the evidence for MACE, TC, LDL-C, total clinical efficacy, the duration of angina attacks, and the frequency of angina attacks were assessed as having moderate certainty. Electrocardiographic efficacy, HDL-C, TG and adverse events were determined to have low certainty. Downgrading was primarily due to risk of bias, inconsistency, and, where applicable, potential publication bias indicated by funnel-plot asymmetry.

3.9 Trial sequential analysis

The cumulative Z-curve for total clinical efficacy crossed the conventional, TSA, and the RIS boundaries, indicating that RCI+WM was superior to Western medicine alone and that this finding is stable. The cumulative Z-curves for the duration of angina attacks, electrocardiographic efficacy, TC, and LDL-C crossed the

conventional and TSA boundaries but did not reach the RIS, suggesting a reliable signal with an information size that is not yet fully met. The cumulative Z-curves for MACE and the frequency of angina attacks crossed the conventional boundary but not the TSA boundary, implying that the accrued sample size remains insufficient and these results should be interpreted cautiously. For TG and HDL-C, the cumulative Z-curves did not cross the conventional boundary and remained far from the TSA/RIS thresholds, indicating that the current evidence is inconclusive. The detailed data related to the sensitivity analysis can be found in Supplementary A 6.

3.10 Machine learning

This study employed Random Forest, XGBoost, Lasso, and MLP as the basic models, and additionally constructed a stacking model by integrating these four base learners. After hyperparameter tuning, all models achieved excellent performance. Model performance was assessed using MSE2, with lower values indicating better predictive accuracy. Overall, Stacking showed the best performance for predicting the optimal treatment duration in UA, whereas Random Forest outperformed the other models in predicting the optimal treatment duration for AMI; detailed results are presented in Table 7.

Overall, RCI treatment duration ranged from 7 to 60 days among 2,610 UA patients and from 7 to 28 days among 1,112 AMI patients, and machine learning methods were applied to estimate the optimal treatment duration for each condition (Table 8), and the model-specific visualization outputs are shown in Figure 14. For UA, the Lasso model suggested that 10.08 days of continuous RCI administration was associated with the most favorable outcomes. For AMI, the model estimated a potential optimal duration of 14.39 days.

4 Discussion

4.1 Interpretation of the results

This meta-analysis included 45 randomized controlled trials involving 4,217 patients with ACS. Because the safety of traditional Chinese medicine injections is often scrutinized, the incidence of adverse events was carefully evaluated. No statistically significant between-group difference was observed in adverse events. Reported adverse events were uncommon and generally mild, such as nausea, dizziness, or headache. These findings suggest that add RCI does not increase safety risks when combined with WM. Nevertheless, continuous post-marketing monitoring and standardized adverse-event reporting remain essential for long-term verification.

In terms of efficacy, RCI + WM demonstrated clear benefits across multiple domains. Compared with WM alone, it significantly reduced the incidence of MACE, decreased the frequency and duration of angina attacks, and improved both total clinical and electrocardiographic efficacy. RCI + WM also produced favorable lipid-modulating effects, mainly reflected in reductions of TC and LDL-C. TG showed no significant between-group difference, and changes in HDL-C were less consistent. Overall, these results suggest that adjunctive RCI may help alleviate ischemia-related symptom burden and facilitate stabilization in the acute phase, while the lipid improvements indicate potential early optimization of atherogenic parameters. TSA indicated that the cumulative evidence for MACE, total clinical

efficacy, electrocardiographic efficacy, and TC was adequate and stable, whereas outcomes for angina and other lipid indices remain underpowered, highlighting the need for larger, longer-term trials.

For machine learning, although available trials have reported treatment courses of 7-28 days, evidence specifically supporting this estimate remains insufficient, meaning the result may be driven by model-based projection rather than directly confirmed by existing data, and thus carries a risk of extrapolation. The MLP model likewise indicated a positive association between RCI efficacy and treatment duration, but based on the current trial evidence, our findings can firmly support only 10.08 days as the optimal duration; accordingly, the 14.39-day value should be interpreted as a theoretical estimate derived from the modeled trend rather than a definitive clinical recommendation. To strengthen the evidence base, future trials should incorporate longer follow-up and more systematically designed treatment courses to evaluate the long-term efficacy and safety of prolonged RCI use in AMI patients.

4.2 Mechanistic evidence

Consistent with our outcomes, the clinical efficacy of RCI appears to derive from multitarget cardioprotective, vasoprotective, antithrombotic, and lipid-regulating actions (Zong et al., 2014; Chen et al., 2022b). Pharmacological and preclinical studies indicate that RCI and its bioactive constituents, particularly salidroside and tyrosol, exert anti-ischemic/anti-hypoxic, antioxidant, anti-inflammatory, and cytoprotective effects while modulating myocardial energy and lipid metabolism, supporting improvements in ischemic symptoms, ECG efficacy, and lipid profiles (Sun et al., 2012). At the vascular level, salidroside improves endothelial function and attenuates atherosclerosis via the AMPK-PI3K-Akt-eNOS pathway, enhancing nitric oxide bioavailability and tissue perfusion (Xing et al., 2015). In myocardial ischemia–reperfusion models, Hongjingtian injection and its constituents reduce infarct size, cardiomyocyte apoptosis, ROS-related autophagic dysregulation, and mitochondrial dysfunction, thereby improving myocardial oxygen utilization and cellular resilience (Zhao et al., 2021).

Regarding thrombosis, salidroside inhibited platelet activation and thrombus formation via suppression of c-Src, Syk, and PLCγ2 phosphorylation, without extending bleeding time, providing a mechanistic rationale for reduced MACE without compromising safety (Wei et al., 2020). Lipid-related and atherosclerotic models further revealed that salidroside lowers serum lipids and plaque burden by downregulating de novo lipogenesis and cholesterol biosynthesis, consistent with our finding that lipid benefits clustered around TC/LDL-C rather than TG (Zhang et al., 2012; Chen et al., 2022b). At the molecular level, salidroside modulates ischemia-reperfusion injury through JNK inhibition and AMPK/PPARα/γ activation, thereby promoting myocardial energy efficiency and lipid homeostasis (Du et al., 2025). Collectively, these mechanisms provide a coherent explanation for the observed improvements in cardiovascular outcomes and overall clinical efficacy associated with adjunctive RCI therapy in ACS.

4.3 Clinical implications

Systematic evidence supporting the use of RCI in ACS remains limited, particularly with respect to the optimal treatment duration and potential differences across ACS subtypes, and its efficacy and safety warrant further evaluation. Our subgroup findings suggest that treatment duration may not materially modify most outcomes, as the short-course (≤10 days) and longer-course (>10 days) groups showed largely comparable benefits among the majority of outcomes. Notably, there was a signal favoring the short-course regimen for reducing the frequency and duration of angina attacks and for improving LDL-C, implying that extending RCI beyond 10 days is unlikely to provide additional clinical benefit and may be unnecessary for most patients. For disease type, given the small evidence base and low certainty, these subgroup signals require confirmation in future trials. Notably, machine learning refined this duration signal by estimating optimal courses of 10.08 days for UA and 14.39 days for AMI, implying that UA may be adequately managed with 10 days, whereas AMI may potentially require a modestly longer course within the range evaluated by current trials. If used, RCI should be positioned strictly as an adjunct to contemporary revascularization and antithrombotic care, rather than a substitute. Given between-study heterogeneity and generally moderate or low certainty of evidence, RCI may be considered selectively, prioritizing UA patients with high symptom burden or adverse lipid profiles and AMI patients at elevated ischemic risk, while adhering to current ACS standards of care.

4.4 Strengths

This study integrate meta-analysis with machine learning. Predictive modeling was used to refine treatment strategies and address the persistent challenge of identifying effective regimens and appropriate durations. Using large-scale aggregated data, this approach supported the therapeutic effect of RCI and provided a quantitative basis for optimizing treatment duration, potentially improving outcomes while reducing unnecessary exposure. Overall, this framework strengthening the evidence base for TCM and supporting broader clinical implementation. In addition, trial sequential analysis was conducted to assess information size and confirm the stability of key findings under sparse-data conditions.

4.5 Limitations

All trials were conducted in one country, limiting generalizability. Intention to treat analyses were rarely reported, and RoB 2 suggested mainly “some concerns” with occasional “high risk,” so benefits may be overestimated and harms underestimated. Residual heterogeneity may reflect variation in concomitant WM regimens. Publication bias and small-study effects are possible, some outcomes were composite or subjective with inconsistent reporting, and long-term patient-important outcomes were scarce, leaving durability uncertain.

4.6 Future perspectives

Given the modest certainty of the evidence, well-designed confirmatory RCTs are warranted. Future studies should be prospectively registered with prespecified analyses, ensure rigorous randomization/allocation concealment, blinded outcome adjudication, and intention-to-treat analyses. They should prioritize long-term, patient-important outcomes (e.g., recurrence and all-cause/cardiovascular mortality)

with predefined safety and patient-reported endpoints. Mechanistic work should further link RCI's PK/PD to biomarkers and omics signatures to support clinical benefit.

5 Conclusion

As an adjunct to WM for ACS, RCI may reduce MACE, improve symptoms and lipid profiles, and maintain a favorable safety profile. The optimal duration of 10.08 days for UA and 14.39 days for AMI, providing preliminary support for RCI as an adjunct in ACS.

Declarations

This study was a systematic review and meta-analysis of previously published studies and did not involve individual patient data or new human participants.

Clinical trial number: Not applicable.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Funding

This research was supported by National Natural Science Foundation of China (grant number 82405612), Tianjin Education Commission Research Program Project (grant number 2023KJ145) and National Key Research and Development Program of China (grant number 2025YFC3507501).

Declaration of competing interest

The authors declare that there are no known financial conflicts of interest or personal relationships that could have influenced the research presented in this paper.

Data availability

Data will be made available on request.

Acknowledgments

We express our gratitude for the financial support provided for this study and acknowledge the contributions of all authors in its successful completion.

Supplementary

Supplementary data to this article can be found online.

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Table 1 Search queries for each database

	Search query for PubMed
#1	"Acute Coronary Syndrome" [MeSH Terms] OR "Acute Coronary Syndromes" [Title/Abstract] OR "Coronary Syndrome, Acute" [Title/Abstract] OR "Coronary Syndromes, Acute" [Title/Abstract] OR "Syndrome, Acute Coronary" [Title/Abstract] OR "Syndromes, Acute Coronary" [Title/Abstract] OR "STEMI" [Title/Abstract] OR "ST Segment Elevation Myocardial Infarction" [Title/Abstract] OR "ST Elevated Myocardial Infarction" [Title/Abstract] OR "NSTEMI" [Title/Abstract] OR "Non ST Elevated Myocardial Infarction" [Title/Abstract] OR "Non-ST-Elevation Myocardial Infarction" [Title/Abstract] OR "Infarction, Non-ST-Elevation Myocardial" [Title/Abstract] OR "Infarctions, Non-ST-Elevation Myocardial" [Title/Abstract] OR "Myocardial Infarction, Non-ST-Elevation" [Title/Abstract] OR "Myocardial Infarctions, Non-ST-Elevation" [Title/Abstract] OR "Non ST Elevation Myocardial Infarction" [Title/Abstract] OR "Non-ST-Elevation Myocardial Infarctions" [Title/Abstract] OR "Angina, Unstable" [Title/Abstract] OR "Anginas, Unstable" [Title/Abstract] OR "Unstable Anginas" [Title/Abstract] OR "Angina at Rest" [Title/Abstract] OR "Angina, Preinfarction" [Title/Abstract] OR "Anginas, Preinfarction" [Title/Abstract] OR "Preinfarction Angina" [Title/Abstract] OR "Preinfarction Anginas" [Title/Abstract] OR "Unstable Angina" [Title/Abstract] OR "Angina Pectoris, Unstable" [Title/Abstract] OR "Angina Pectori, Unstable" [Title/Abstract] OR "Unstable Angina Pectori" [Title/Abstract] OR

	"Unstable Angina Pectoris" [Title/Abstract] OR "Myocardial Preinfarction Syndrome" [Title/Abstract] OR "Myocardial Preinfarction Syndromes" [Title/Abstract] OR "Preinfarction Syndrome, Myocardial" [Title/Abstract] OR "Preinfarction Syndromes, Myocardial" [Title/Abstract] OR "Syndrome, Myocardial Preinfarction" [Title/Abstract] OR "Syndromes, Myocardial Preinfarction" [Title/Abstract]
#2	"*Rhodiola crenulata*" [MeSH Terms] OR "*Rhodiola rosea*" [Title/Abstract] OR "*Roseroot*" [Title/Abstract] OR "*Roseroots*" [Title/Abstract] OR "Hongjingtian" [Title/Abstract] OR "Hong jing tian" [Title/Abstract]
#3	"randomized controlled trial" [Publication type] OR "randomized clinical trial" [Publication type] OR "randomized trial" [Publication type] OR "clinical trial" [Publication type] OR "randomized controlled trial" [Title/Abstract] OR "randomized clinical trial" [Title/Abstract] OR "randomized trial" [Title/Abstract] OR "clinical trial" [Title/Abstract]
#4	#1 AND #2 AND #3

Table 2 Characteristics of included trials

Study	Disease	Age (T/C)	Sample size (T/C)	Course of the disease (T/C)	Intervention (T/C)	Dose in the experimental group	Course of treatment (days)	Outcome
(Wang and Yang, 2018)	UA	49.3 ± 11.9/52.6 ± 10.3	130/130	-	RCI + WM / WM	10 mL/qd	14d	③
(Zhu, 2019)	UA	70.25 ± 10.88/59.98 ± 11.06	32/32	4.30 ± 1.59/4.25 ± 1.75 years	RCI + WM / WM	10 mL/qd	15d	④

(Li and Chen, 2018)	UA	58.21 ± 7.61/57.90 ± 7.04	38/38	4.65 ± 1.48/4.31 ± 1.27 years	RCI + WM	WM	10 mL/qd	28d	④
(Wang et al., 2018)	UA	58 ± 7.1/57.2 ± 7.3	60/58	-	RCI + WM	WM	10 mL/qd	14d	③④
(Zhang, 2013)	UA	58.72 ± 12.86/60.72 ± 11.56	42/41	5.3 ± 1.6/5.2 ± 1.5 years	RCI + WM	WM	10 mL/qd	10d	③④
(Cao, 2019)	UA	61.4 ± 3.3/60.3 ± 3.4	47/47	5.3 ± 1.6/5.2 ± 1.5 years	RCI + WM	WM	10 mL/qd	-	③
(Hao, 2016)	UA	-	30/30	-	RCI + WM	WM	10 mL/qd	7d	③
(Kong and Su, 2016)	UA	-	30/30	-	RCI + WM	WM	10 mL/qd	28d	③
(Jia and Wang, 2014)	UA	35–76/35–76	45/42	-	RCI + WM	WM	10 mL/qd	10d	③④
(Li and Lu, 2020)	UA	52.84 ± 4.17/51.28 ± 3.44	68/68	1.37 ± 0.87/1.23 ± 0.91 years	RCI + WM	WM	10 mL/qd	10d	①②④⑥⑧⑨
(Li et al., 2021)	UA	70.36 ± 3.66/70.33 ± 3.64	62/61	3.31 ± 1.24/3.23 ± 1.11 years	RCI + WM	WM	10 mL/qd	60d	④⑥⑦⑨
(Li et al., 2015)	UA	48–80/48–81	50/50	-	RCI + WM	WM	5 mL/qd	7d	①②③④⑤
(Li and Zhao, 2014)	UA	57.5 ± 5.6/58.1 ± 5.2	40/40	-	RCI + WM	WM	10 mL/qd	15d	③
(Wang et al., 2015)	UA	54 ± 3/55 ± 4	40/40	-	RCI + WM	WM	10 mL/qd	14d	③
(Wang zhi et al., 2020)	UA	56.38 ± 13.53/54.96 ± 14.29	77/77	8.49 ± 2.41/8.02 ± 2.64 years	RCI + WM	WM	10 mL/qd	14d	①②③
(Weng et al., 2015)	UA	66 ± 6/65 ± 8	61/62	2–10 years/6 months–8.5 years	RCI + WM	WM	10 mL/qd	10d	①③⑥⑦⑧⑨
(Huang	UA	67.30 ±	30/30	7.6 ± 5.9/7.3	RCI	W	10 mL/qd	14d	③⑤

and Zhang, 2016)		4.89/66.40 ± 5.96		± 5.56 years	+ WM	M			
(Zhang, 2012)	UA	59.74 ± 10.77/60.69 ± 11.72	45/43	3–6/3–7 years	RCI + WM	WM	10 mL/qd	10d	③④
(Cao et al., 2023)	UA	69.29 ± 5.87/70.24 ± 6.18	49/49	-	RCI + WM	WM	10 mL/qd	10d	④⑤
(Du, 2017)	UA	70.45 ± 9.83/71.02 ± 9.79	40/40	-	RCI + WM	WM	10 mL/qd	10d	④
(Chen, 2013)	UA	61–84/61–83	30/30	5.5 ± 3.4/5.4 ± 3.6 years	RCI + WM	WM	10 mL/qd	14d	①②③④⑤
(Ou et al., 2019)	UA	68.76 ± 7.41/68.27 ± 5.66	39/35	7.94 ± 3.67/7.29 ± 2.46 years	RCI + WM	WM	10 mL/qd	14d	①②③④⑤
(Tian et al., 2016)	UA	35–74/38–78	40/40	-	RCI + WM	WM	10 mL/qd	14d	③
(Zhang pu, 2013)	AMI	56.1 ± 10.2/55.8 ± 10.4	59/59	-	RCI + WM	WM	10 mL/qd	14d	③
(Xu et al., 2016)	AMI	52–74/53–72	40/38	-	RCI + WM	WM	10 mL/qd	14d	③
(Xian et al., 2015)	AMI	60.7 ± 10.2/61. 3 ± 9.8	49/49	-	RCI + WM	WM	10 mL/qd	14d	③④
(Hou et al., 2018)	AMI	51.4 ± 7.6/51.4 ± 7.6	31/31	-	RCI + WM	WM	10 mL/qd	14d	⑥⑦⑧⑨
(Zhao and Chen, 2017)	ACS	59.42 ± 11.27/59.99 ± 11.67	56/56	18.54 ± 8.51/18.01 ± 8.27 h	RCI + WM	WM	10 mL/qd	14d	④
(Fan, 2018)	ACS	52.58 ± 12.03/51.02 ± 11.28	55/55	18.01 ± 3.96/16.88 ± 4.54 h	RCI + WM	WM	10 mL/qd	14d	④⑤
(Peng et al., 2019)	ACS	56.22 ± 10.3/54.97 ± 10.2	52/52	1.15 ± 0.19/1.13 ± 0.21 years	RCI + WM	WM	10 mL/qd	14d	④⑤⑥⑦⑧⑨
(Yang et	AC	62.9 ±	42/42	43.1 ±	RCI	W	10 mL/qd	10d	④

al., 2019)	S	4.1/63.1 ± 4.3		4.4/42.5 ± 4.8 h	+ WM	M			
(Hu, 2015)	ACS	49.3 ± 7.2/48.6 ± 6.8	49/49	-	RCI + WM	WM	10 mL/qd	14d	⑥⑦⑨
(Li and He, 2016)	ACS	63.87 ± 10.46/63.85 ± 9.51	30/20	-	RCI + WM	WM	10 mL/qd	3-7d	④⑤⑥⑦⑧⑨
(Liu, 2017)	ACS	59.42 ± 11.27/59.99 ± 11.67	56/56	18.54 ± 8.51/18.01 ± 8.27 h	RCI + WM	WM	10 mL/qd	14d	④
(Liu, 2015)	AMI	62.3 ± 6.4/61.5 ± 8.1	70/70	13.9 ± 2.2/14.1 ± 2.2 years	RCI + WM	WM	10 mL/qd	10d	④
(Ji and Liu, 2018)	AMI	51.4 ± 5.1/49.3 ± 4.6	40/40	-	RCI + WM	WM	10 mL/qd	14d	④
(Shi et al., 2014)	AMI	56.1 ± 8.2/54.7 ± 9.3	58/57	-	RCI + WM	WM	10 mL/qd	14d	⑨
(Chen et al., 2014)	AMI	59.50 ± 7.55/59.10 ± 7.32	42/40	-	RCI + WM	WM	10 mL/qd	14d	④⑥⑦⑧⑨
(Dong, 2020)	NSTEMI	70.5 ± 4.8/72.4 ± 3.5	50/50	-	RCI + WM	WM	10 mL/qd	14d	③
(Chen et al., 2014)	NSTEMI	59.82 ± 10.55/60.12 ± 10.72	30/31	-	RCI + WM	WM	10 mL/qd	10d	④
(Wang and Liu, 2018)	AMI	66.3 ± 8.2/67.1 ± 8.6	49/49	5.3 ± 1.2/5.2 ± 1.3 years	RCI + WM	WM	10 mL/qd	14d	④
(Li et al., 2017)	ACS	66.7 ± 12.4/67.1 ± 11.6	36/35	-	RCI + WM	WM	20 mL/qd	10d	④
(Zhang and Lu, 2016)	UA	60 ± 7/61 ± 8	27/27	-	RCI + WM	WM	10 mL/qd	14d	①②④
(Zhang et al., 2018)	UA	60.7 ± 6.5/59.8 ± 6.9	63/63	3.5 ± 1.3/3.2 ± 1.6 years	RCI + WM	WM	10 mL/qd	14d	④⑧⑨
(Wang, 2017)	NSTEMI	63.8 ± 11.7/62.2 ± 10.4	40/40	-	RCI + WM	WM	10 mL/qd	10d	③⑩

Abbreviations: qd, once daily; mL, milliliter; UA, unstable angina; AMI, acute myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; ACS, acute coronary syndrome; T, treatment group; C, control group; RCI, *Rhodiola crenulata injection*; WM, western medicine. ①, The frequency of angina attacks; ②, The duration of angina attacks; ③, Electrocardiographic efficacy; ④, Total clinical efficacy; ⑤, Adverse events; ⑥, Total cholesterol (TC); ⑦, Triglycerides (TG); ⑧, High-density lipoprotein cholesterol (HDL-C); ⑨, Low-density lipoprotein cholesterol (LDL-C); ⑩, Major adverse cardiovascular events (MACE)

Table 3 Incidence of adverse events

Study	Sample size		Adverse events	
	T	C	T	C
(Cao et al., 2023)	49	49	6 (2 nausea, 1 headache, 1 dizziness, 2 inappetence)	4 (2 dizziness, 1 headache, 1 inappetence)
(Chen, 2013)	30	30	0	0
(Chen et al., 2014)	42	40	3 (2 mild gastrointestinal hemorrhage, 1 gum bleeding)	2 (1 mild gastrointestinal hemorrhage, 1 hemoptysis)
(Fan, 2018)	65	65	0	0
(Huang and Zhang, 2016)	30	30	0	0
(Li et al., 2015)	50	50	0	0
(Li et al., 2021)	62	61	1 (asthenia)	2 (1 palpitation, 1 dizziness)
(Liu, 2015)	70	70	0	0
(Ou et al., 2019)	39	35	0	0
(Peng et al., 2019)	52	52	7 (1 dizziness, 2 abdominal distension, 1 vascular pain, 3 skin itch)	5 (1 dizziness, 1 ventosity, 2 vascular pain, 1 skin itch)
(Weng et al., 2015)	61	62	2 (2 dizziness and headache)	1 (dizziness and headache)
(Zhang et al., 2018)	63	63	3 (1 dizziness, 1 chill, 1 nausea)	2 (1 dizziness, 1 nausea)

Table 4 Subgroup analysis based on the treatment duration

Outcome	**Subgroup**	**Number of studies**	**Sample Size (T/C)**	**Measures**	**Effect estimate (95% CI)**	**Heterogeneity (I^2)**	$P_{interaction}$
MACE	≤10d	2	110/110	RR	0.57 [0.38, 0.86]	0%	0.89
	>10d	1	40/40	RR	0.55 [0.31, 0.95]	-	
The frequency of angina attacks	≤10d	3	179/180	MD	-2.88 [-4.10, -1.66]	93%	0.001
	>10d	4	173/169	MD	-0.46 [-1.32, 0.40]	89%	
The	≤10d	2	118/118	MD	-3.95 [-6.47,	87%	0.02

duration of angina attacks					-1.42]		
	>10d	4	173/169	MD	-0.83 [-1.01, -0.64]	0%	
Total clinical efficacy	≤10d	12	547/531	RR	1.28 [1.21, 1.36]	0%	0.07
	>10d	15	718/711	RR	1.20 [1.14, 1.25]	21%	
Electrocardiographic efficacy	≤10d	7	313/308	RR	1.27 [1.06, 1.53]	81%	0.95
	>10d	14	714/706	RR	1.25 [1.17, 1.35]	38%	
TC	≤10d	2	129/130	MD	-0.98 [-1.69, -0.28]	66%	0.37
	>10d	5	235/233	MD	-0.64 [-0.90, -0.37]	73%	
TG	≤10d	1	61/62	MD	-0.26 [-0.62, 0.10]	-	0.60
	>10d	5	235/233	MD	-0.15 [-0.36, 0.07]	86%	
LDL-C	≤10d	2	129/130	MD	-0.89 [-1.32, -0.45]	35%	0.03
	>10d	7	356/353	MD	-0.35 [-0.54, -0.16]	87%	
HDL-C	≤10d	2	129/130	MD	0.34 [0.17, 0.52]	40%	0.33
	>10d	4	188/186	MD	0.16 [-0.18, 0.49]	96%	
Adverse events	≤10d	4	230/231	RR	1.61 [0.55, 4.69]	0%	0.72
	>10d	8	383/376	RR	1.26 [0.59, 2.69]	0%	

Abbreviations: C, control group; T, treatment group; d, day; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MD, mean difference; P interaction, P for interaction; RR, relative risk; TC, total cholesterol; TG, triglycerides.

Table 5 Subgroup analysis based on disease type

Outcome	Subgroup	Number of study	Sample Size (T/C)	Measures	Effect estimate (95% CI)	Heterogeneity (I^2)	$P_{interaction}$
Total clinical efficacy	UA	15	690/677	RR	1.22 [1.17, 1.28]	30%	0.03
	AMI	5	238/239	RR	1.40 [1.25, 1.57]	32%	
Electrocardiographic	UA	16	806/796	RR	1.23 [1.13, 1.34]	65%	0.96

efficacy	AMI	5	221/218	RR	1.22 [0.94, 1.59]	82%	
Adverse events	UA	8	384/380	RR	1.33 [0.58, 3.08]	0%	0.94
	AMI	1	42/40	RR	1.43 [0.25, 8.11]	-	
TC	UA	3	191/191	MD	-0.92 [-1.29, -0.54]	57%	0.55
	AMI	1	42/40	MD	-0.60 [-1.56, 0.36]	-	
TG	UA	2	123/123	MD	-0.25 [-0.36, -0.14]	0%	0.0005
	AMI	2	73/71	MD	0.06 [-0.08, 0.19]	0%	
LDL-C	UA	4	254/254	MD	-0.54 [-1.03, -0.05]	98%	0.50
	AMI	3	131/128	MD	-0.32 [-0.73, 0.10]	92%	
HDL-C	UA	3	192/193	MD	0.05 [-0.54, 0.63]	97%	0.60
	AMI	2	73/71	MD	0.20 [0.15, 0.25]	0%	

Abbreviations: C, control group; T, treatment group; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MD, mean difference; AMI, acute myocardial infarction; P interaction, P for interaction; RR, relative risk; TC, total cholesterol; TG, triglycerides; UA, unstable angina.

Table 6 Certainty of evidence

Outcome	**Quality assessment**							**No. of patients**		**Effect**		**Certainty**
	No. of trials	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**T**	**C**	**Relative (95% CI)**	**Absolute (95% CI)**	
MACE	3	RCT	serious	no serious	no serious	no serious	none	36/150 (24%)	64/150 (42.7%)	RR 0.56 (0.4 to 0.78)	188 fewer per 1000 (from 94 fewer to 256 fewer)	⊕⊕⊕○ MODERATE
The frequency of angina	7	RCT	serious	no serious	no serious	no serious	none	352	349	-	MD 1.63 lower (3.11 to 0.16 lower)	⊕⊕⊕○ MODERATE

attacks												
The duration of angina attacks	6	RCT	serious	no serious	no serious	no serious	none	291	287	-	MD 1.76 lower (2.52 to 1 lower)	⊕⊕⊕○ MODERATE
Total clinical efficacy	27	RCT	serious	no serious	no serious	no serious	none	1154/1265 (91.2%)	919/1242 (74%)	RR 1.23 (1.19 to 1.28)	170 more per 1000 (from 141 more to 207 more)	⊕⊕⊕○ MODERATE
Electrocardiographic efficacy	22	RCT	serious	serious	no serious	no serious	none	851/1074 (79.2%)	655/1061 (61.7%)	RR 1.24 (1.16 to 1.33)	148 more per 1000 (from 99 more to 204 more)	⊕⊕○○ LOW
Adverse events	12	RCT	serious	no serious	no serious	serious	none	22/613 (3.6%)	16/607 (2.6%)	RR 1.37 (0.74 to 2.54)	10 more per 1000 (from 7 fewer to 41 more)	⊕⊕○○ LOW
TC	7	RCT	serious	no serious	no serious	no serious	none	364	363	-	MD 0.73 lower (1 to 0.46 lower)	⊕⊕⊕○ MODERATE
TG	6	RCT	serious	no serious	no serious	serious	none	296	295	-	MD 0.16 lower (0.36 lower to 0.03 higher)	⊕⊕○○ LOW
LDL-C	9	RCT	serious	no serious	no serious	no serious	none	485	483	-	MD 0.43 lower (0.74 to 0.13 lower)	⊕⊕⊕○ MODERATE
HDL-C	6	RCT	serious	serious	no serious	no serious	none	317	316	-	MD 0.2 higher (0.01 to 0.39 higher)	⊕⊕○○ LOW

Abbreviations: C, control group; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; P interaction, P for interaction; RR, relative risk; T, treatment group; TC, total cholesterol;

TG, triglycerides; UA, unstable angina.

Table 7 Specific data on MSE2 for each machine learning model.

Disease type	Random Forest	XGBoost	Lasso	MLP	Stacking
UA	0.249816	0.480286	0.392798	0.339463	0.162407
AMI	0.162398	0.123233	0.446470	0.340446	0.383229

Table 8 Optimal treatment duration predicted using different machine learning models.

Category	Random Forest	XGBoost	Lasso	MLP	Stacking
UA	26.85	38.73	10.08	44.53	51.12
AMI	16.72	29.89	14.39	31.17	34.25

Figure 1. Flow diagram of study screening

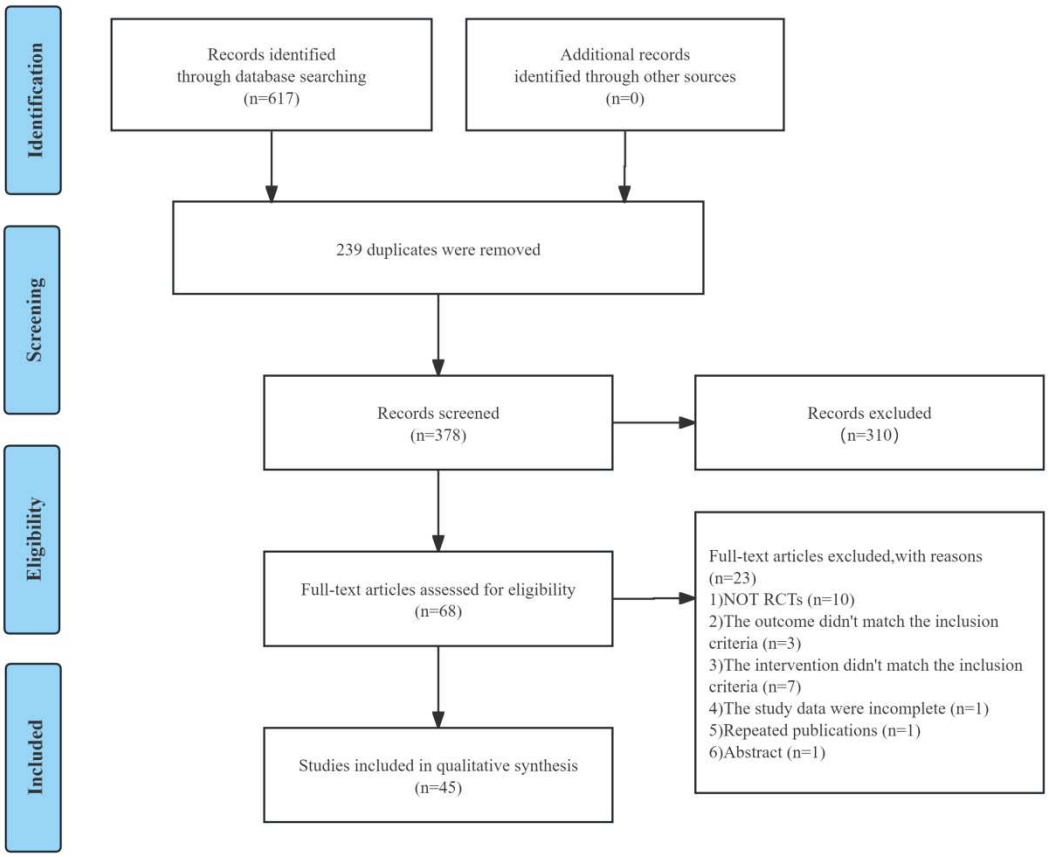


Figure 2 Risk of bias graph

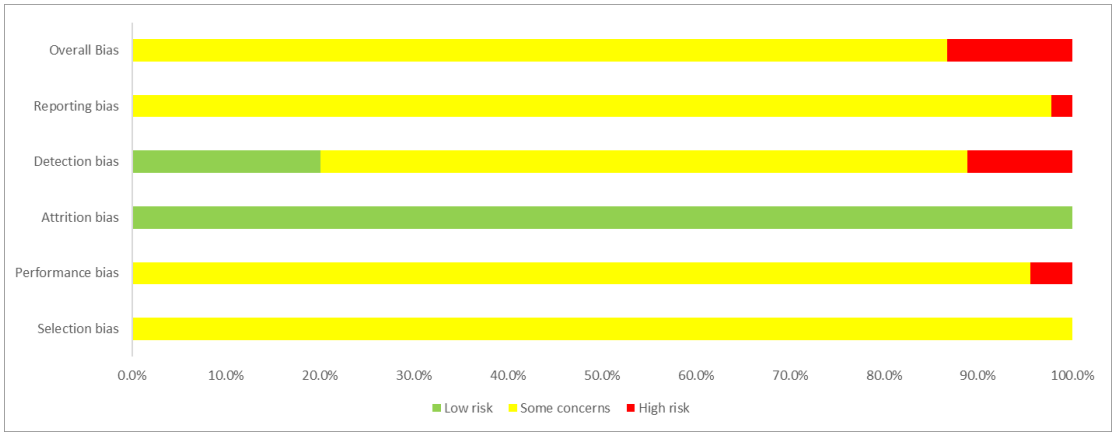


Figure 3. Meta-analysis results of major adverse cardiovascular events

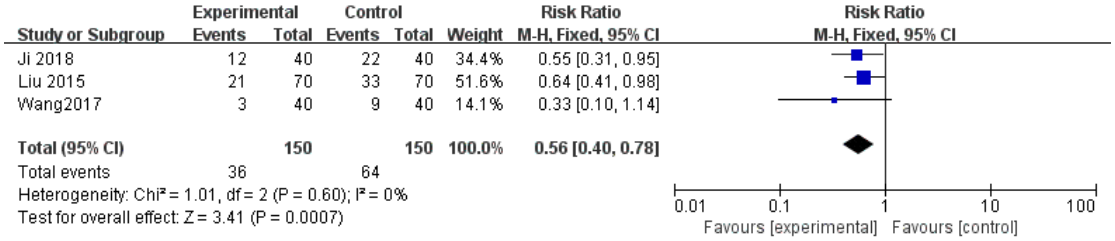


Figure 4. Meta-analysis results of the frequency of angina attacks

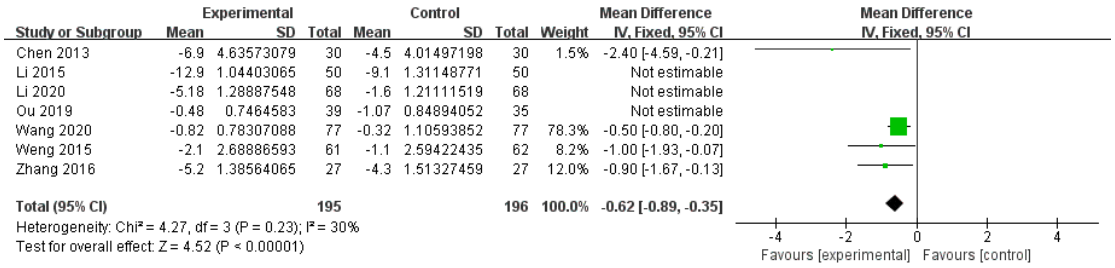


Figure 5. Meta-analysis results of the duration of angina attacks

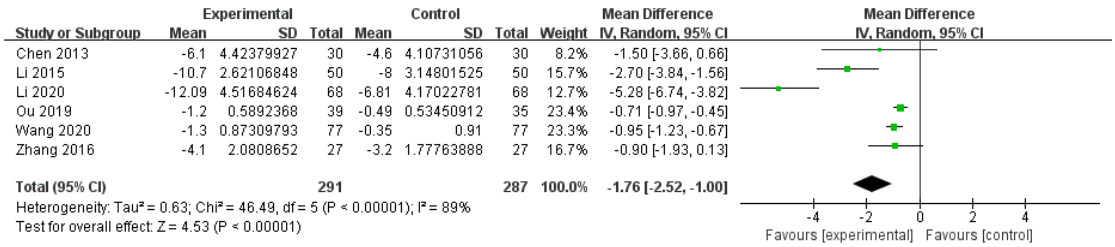


Figure 6. Meta-analysis results of total clinical efficacy

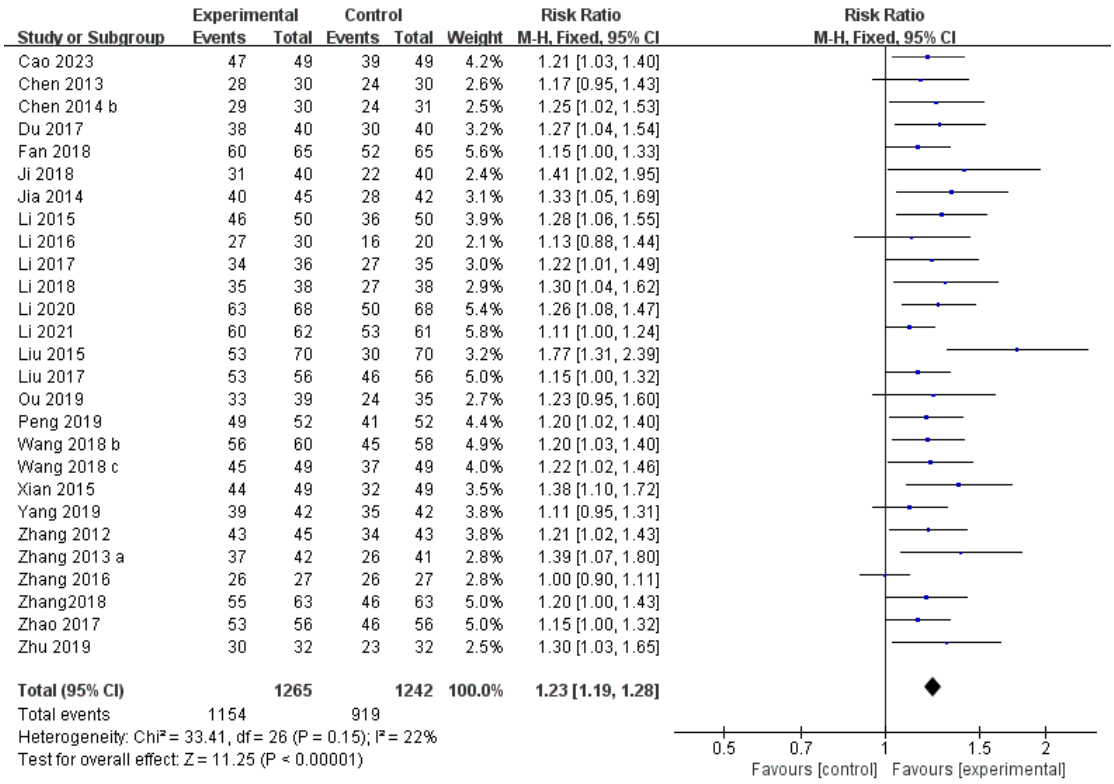


Figure 7. Meta-analysis results of electrocardiographic efficacy

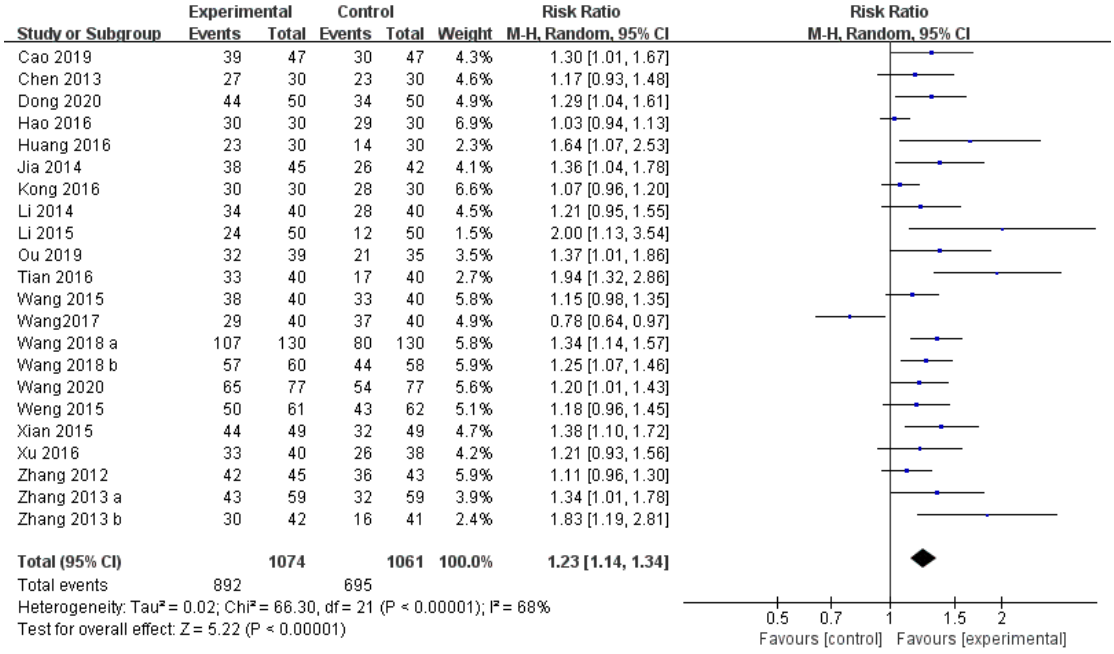


Figure 8. Meta-analysis results of the total cholesterol (TC)

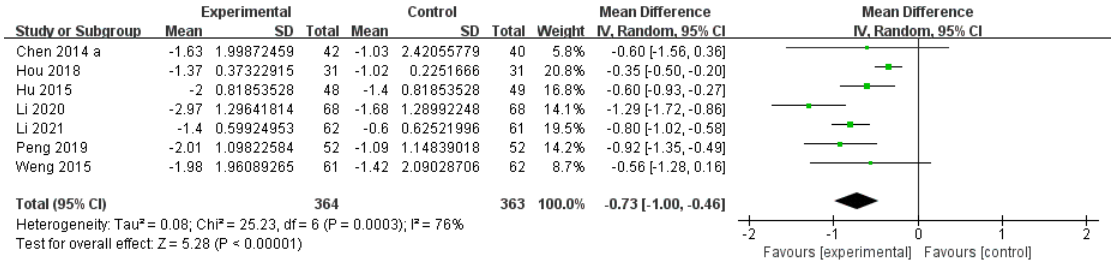


Figure 9. Meta-analysis results of the triglycerides (TG)

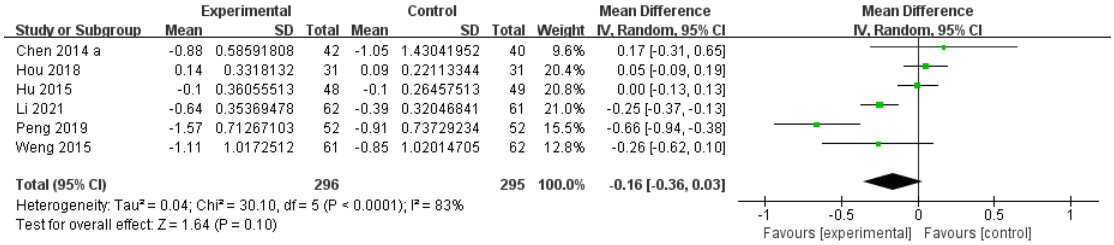


Figure 10. Meta-analysis results of the high-density lipoprotein cholesterol (HDL-C)

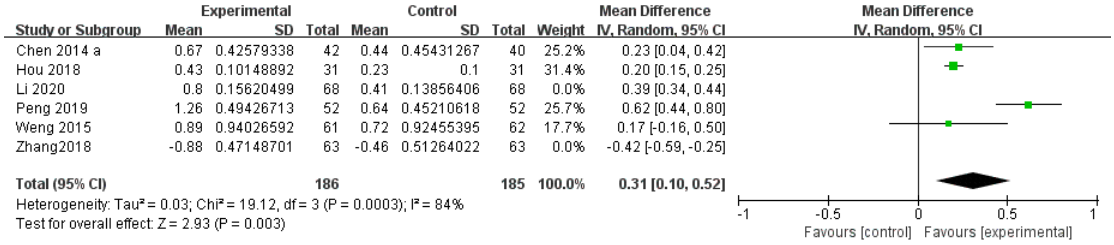


Figure 11. Meta-analysis results of the low-density lipoprotein cholesterol (LDL-C)

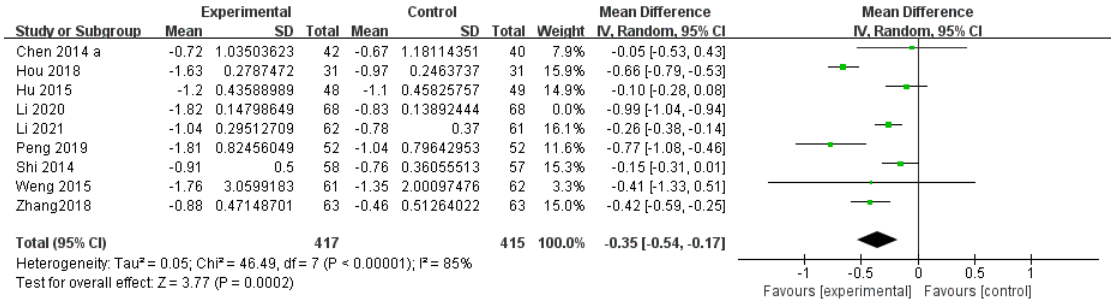


Figure 12. Meta-analysis results of adverse events

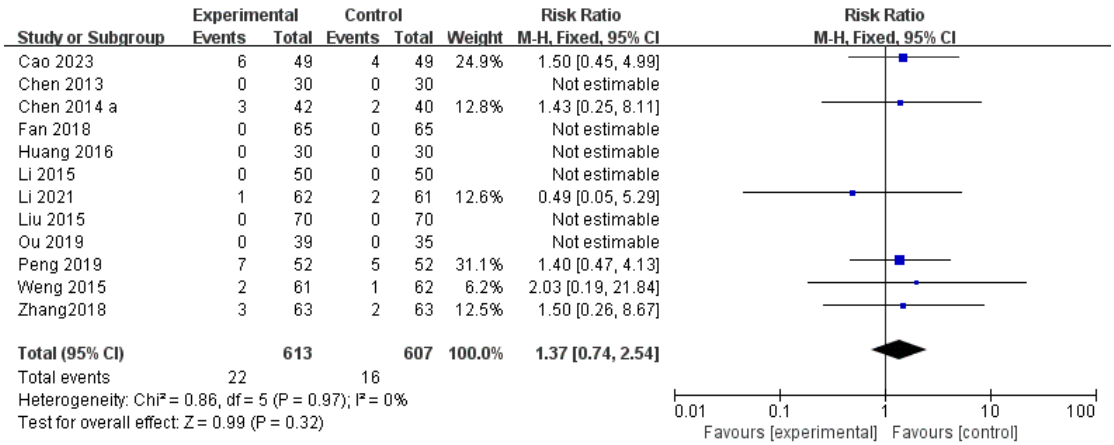


Figure 13A electrocardiographic efficacy

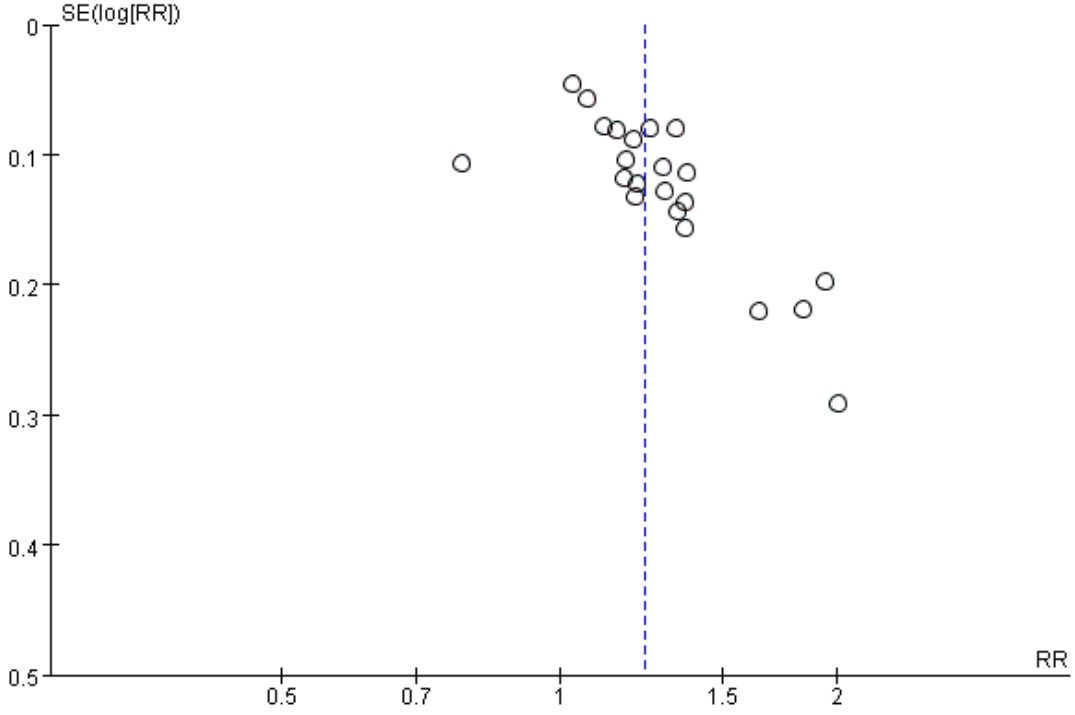


Figure 13B Total clinical efficacy

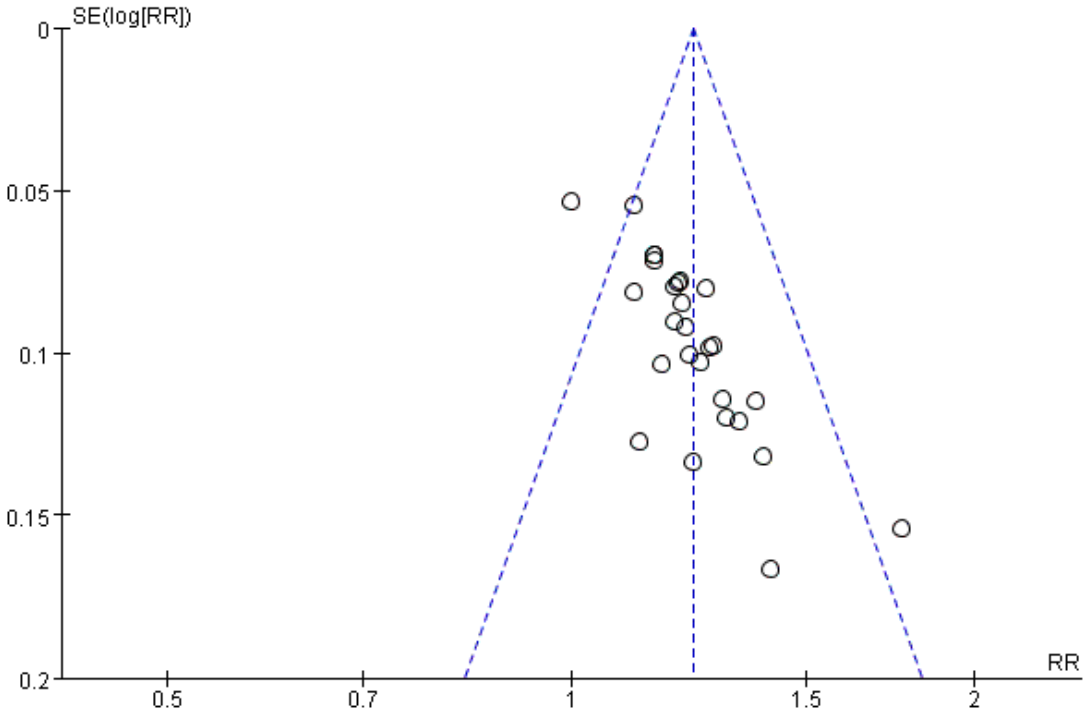
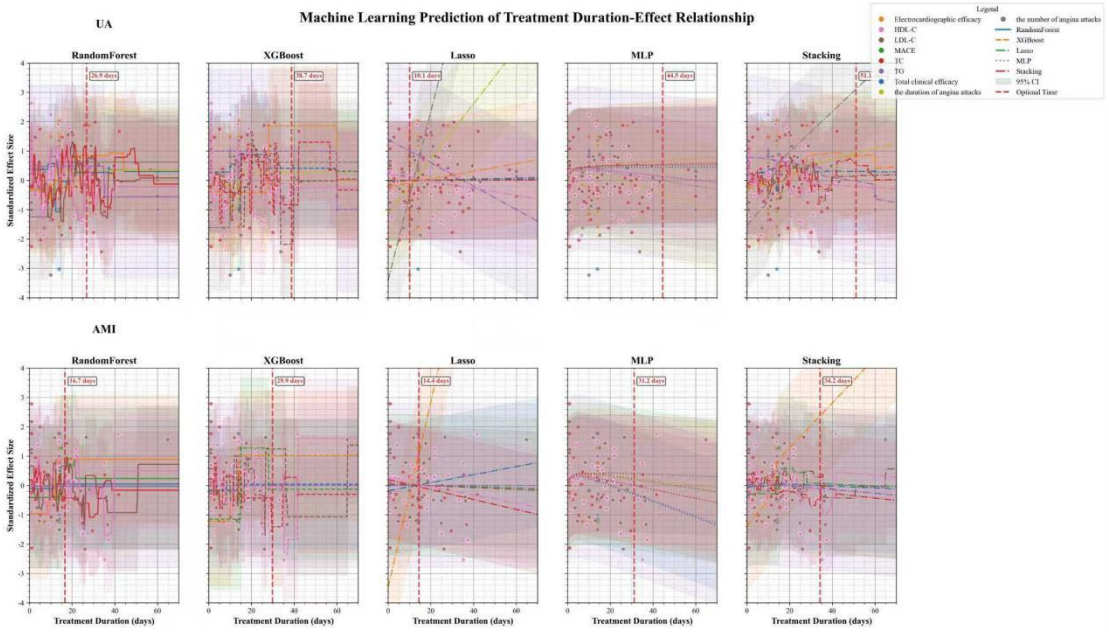


Figure 14 Predicted optimal treatment duration for each disease using different machine learning models (from left to right, Random Forest, XGBoost, Lasso, MLP, Stacking).



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