Original Article

Ranolazine for improving coronary microvascular function in patients with nonobstructive coronary artery disease: a systematic review and meta-analysis with a trial sequential analysis of randomized controlled trials

Hao Ling[1], Sunjing Fu[2,3], Mengting Xu[2,3], Bing Wang[2,3], Bingwei Li[2,3], Yuan Li[2,3], Xueting Liu[2,3], Xiaoyan Zhang[2,3], Qin Wang[2,3], Ailing Li[2,3], Mingming Liu[2,3,4]

[1]Department of Radiology, The Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China, Changsha, China; [2]Institute of Microcirculation, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [3]International Center of Microvascular Medicine, Chinese Academy of Medical Sciences, Beijing, China; [4]Diabetes Research Center, Chinese Academy of Medical Sciences, Beijing, China

Contributions: (I) Conception and design: M Liu; (II) Administrative support: M Liu; (III) Provision of study materials or patients: H Ling, S Fu, M Xu, B Wang; (IV) Collection and assembly of data: B Li, Y Li, X Liu, X Zhang; (V) Data analysis and interpretation: H Ling, S Fu, Q Wang, A Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mingming Liu, PhD. Institute of Microcirculation, Chinese Academy of Medical Sciences & Peking Union Medical College, 5 Dong-Dan Third Alley, Beijing 100005, China; International Center of Microvascular Medicine, Chinese Academy of Medical Sciences, 5 Dong-Dan Third Alley, Beijing 100005, China; Diabetes Research Center, Chinese Academy of Medical Sciences, 5 Dong-Dan Third Alley, Beijing 100005, China; Email: mingmingliu@imc.pumc.edu.cn.

Background: Microvascular dysfunction in patients with nonobstructive coronary artery disease is increasingly being recognized as an important health issue. This systematic review and meta-analysis evaluated the effectiveness of ranolazine, an antianginal agent, in improving coronary microvascular function.

Methods: We conducted a comprehensive literature search of the Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure, the Chinese BioMedical Literature Database, and gray literature databases until September 30, 2023. The included studies were randomized controlled trials (RCTs) published in the English or Chinese languages that screened for eligibility using two independent investigators. Risk of bias was evaluated with the Cochrane Collaboration tool. Subgroup and sensitivity analyses were used to identify sources of heterogeneity. Meta-analysis was performed using RevMan version 5.4 (Cochrane) and Stata version 16.0 (StataCorp).

Results: From 1,470 citations, 8 RCTs involving 379 participants were included in this analysis. Our findings showed that ranolazine increased coronary flow reserve (CFR) over an 8 to 12-week follow-up period [standardized mean difference =1.16; 95% confidence interval (CI): 0.4–1.89; P=0.002]. Ranolazine increased the global myocardial perfusion reserve index (MPRI) [weighted mean difference (WMD) =0.18; 95% CI: 0.07–0.29; P=0.002] and the midsubendocardial MPRI (WMD =0.10; 95% CI: 0.02–0.19; P=0.02). Moreover, ranolazine improved 3 of the 5 Seattle Angina Questionnaire scores, namely, physical functioning (WMD =4.89; 95% CI: 0.14 to 9.64; P=0.04), angina stability (WMD =17.31; 95% CI: 7.13–27.49; P=0.0009), and quality of life (WMD =10.11; 95% CI: 3.57–16.65; P=0.0003). Trial sequential analysis showed that the meta-analysis of angina stability and quality of life scores had a sufficient sample size and statistical power.

Conclusions: Our analysis suggests that ranolazine is associated with improvements in CFR, myocardial perfusion, and the Seattle Angina Questionnaire scores in patients with nonobstructive coronary artery disease. However, further large-scale RCTs with long-term follow-up are recommended to validate

these findings and provide a more comprehensive understanding of the effects of ranolazine on coronary microvascular function.

Keywords: Ranolazine; coronary microvascular dysfunction (CMD); coronary microvascular function; coronary flow reserve (CFR); myocardial perfusion reserve index (MPRI)

Submitted Jul 20, 2023. Accepted for publication Nov 23, 2023. Published online Jan 09, 2024.
doi: 10.21037/qims-23-1029
View this article at: https://dx.doi.org/10.21037/qims-23-1029

Introduction

Recently, a growing recognition has emerged regarding patients who exhibit symptoms of myocardial ischemia but lack coronary artery obstruction (1). Microvascular angina is a prevalent symptomatic manifestation of transient myocardial ischemia and has been confirmed to result from microvascular dysfunction with nonobstructive coronary artery disease. As one of the endotypes of ischemia with unobstructed coronary arteries (2), microvascular angina results from coronary vasospasm and microvascular dysfunction. However, treatment of microvascular angina symptoms is extremely challenging due to its unclear pathophysiological mechanism and a lack of homogeneous randomized controlled trials (RCTs) with large sample sizes.

The "Diamond approach" (3), an expert-proposed algorithm, involves the personalized treatment of symptomatic angina, factoring in comorbidities and potential mechanisms of transient myocardial ischemia. The treatment mainly leverages first-line (calcium-channel blockers, β-blockers, short-acting nitrates) or second-line drugs (nicorandil, ranolazine, ivabradine, trimetazidine). Pharmacological treatment of coronary microvascular dysfunction (CMD) poses challenges, as 20–30% of patients remain symptomatic despite first-line antianginal treatment (4). In such instances, second-line drugs, approved based on rigorous protocols and cohort data from long-term follow-up studies (5), are recommended as monotherapy or in combination therapy, especially when contraindications exist.

Ranolazine, a second-line antianginal drug, inhibits late sodium channels, preventing intracellular calcium overload, thus improving diastolic tension, myocyte relaxation, and angina symptoms (6). CMD may be secondary to changes in the microcirculation or vasomotor dysfunction. The failure of the coronary vasculature to augment blood flow in response to increased myocardial demand, defined as impaired coronary flow reserve (CFR) (7), is a diagnostic method recommended by the European Society of Cardiology guidelines (8) for identifying patients with microvascular angina. Our study chose ranolazine over other second-line drugs such as nicorandil or ivabradine due to its unique inhibitory action in the late phase of the inward sodium current in cardiac myocytes, which reduces myocardial oxygen demand without significantly affecting heart rate or blood pressure (9,10). Ranolazine is considered for patients with refractory angina who are intolerant to other antianginal therapy (11). Moreover, it generally has a side-effect profile that is well-tolerated, especially in contrast to, for example, nicorandil's association with ulcerative complications and ivabradine's potential to cause bradycardia (12,13). Nevertheless, ranolazine's effects on nonobstructive coronary artery disease are unclear, with discrepant findings being reported in previous meta-analyses regarding CFR improvement (14-16). Myocardial perfusion reserve index (MPRI), an imaging marker of small-vessel vasodilation capacity, has shown varied responses to ranolazine treatment (17-19). Thus, the effects of ranolazine on CFR and MPRI remain a subject of debate, with insufficient research on treatment time and drug dose effects on CFR via subgroup analysis.

Given the inconsistencies among different meta-analyses, our study applied evidence-based medicine principles to evaluate RCTs of individuals with nonobstructive coronary artery disease to assess ranolazine's effectiveness in improving coronary microvascular function. This article is presented in accordance with the PRISMA reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1029/rc).

Methods

Search strategy

Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), and the Chinese

BioMedical Literature Database (CBM) were searched for published RCTs in English or Chinese languages. The keywords were "ranolazine", "late sodium channel blocker", "nonobstructive coronary artery disease", "ischemia with nonobstructive coronary arteries", "coronary microvascular dysfunction", "microvascular angina", "angina with nonobstructive coronary arteries", "microcirculatory function", and "cardiac syndrome X". We conducted our final searches on the databases on the following dates: the Cochrane Library on September 29, 2023; PubMed on September 30, 2023; Embase on September 30, 2023; CNKI on September 30, 2023; and CBM on September 30, 2023. Furthermore, in our pursuit of comprehensive data collection, we made a concerted effort to include potentially relevant studies that might have reported negative results. To this end, we extended our search to gray literature databases, specifically OpenGrey and the Healthcare Management Information Consortium (HMIC). This strategy was instrumental in ensuring the breadth and inclusivity of our research scope. The search terms are listed in detail in Table S1. The meta-analysis protocol and systematic search strategy are registered in PROSPERO (International Prospective Register of Systematic Reviews; registration ID: CRD42022298144).

Study selection

Studies were independently selected by two investigators (Y Li and XT Liu). Any disparities in study selection were resolved through consultation between the two investigators or with deference to a third reviewer (BW Li). The inclusion criteria were as follows: (I) RCTs on individuals with nonobstructive coronary artery disease indicated by invasive assessment (e.g., coronary angiography); (II) studies of ranolazine treatment for individuals with nonobstructive coronary artery disease; (III) studies including assessment of coronary microcirculatory function assessment (CFR and/or MPRI); and (IV) studies in which the outcome measure was the Seattle Angina Questionnaire (SAQ), including the physical functioning, angina stability, quality of life, angina frequency, and treatment satisfaction scores. Due to language proficiency of the review team, we included in the analysis only those studies that were published in English or Chinese. The exclusion criteria were as follows: (I) reviews, editorials, letters, case reports, meta-analyses, and animal studies; (II) non-RCTs; (III) studies of obstructive coronary artery disease; (IV) studies that did not assess coronary microvascular function; and (V) studies whose full text or data could not be obtained.

Data extraction

Two investigators performed the data extraction independently. Discrepancies were resolved through consultation between the two investigators (SJ Fu and MT Xu) or with deference to a third investigator (H Ling). Data on the lead author, publication date, study design, study size, follow-up period, inclusion and exclusion criteria, method of coronary microvascular function assessment, dosage, and duration of ranolazine were extracted from the RCTs. The included RCTs were evaluated in 7 domains of risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias) in accordance with the Cochrane Collaboration.

Statistical analysis

The meta-analysis was performed with RevMan version 5.4 (Cochrane) and Stata version 16.0 (StataCorp). Summary results for CFR or MPRI outcome data are presented as the standardized mean difference (SMD) or weighted mean difference (WMD) with 95% confidence intervals (CIs) for different measurement methods. The chi-squared Q test and I^2 statistics were reflected in the assessment of heterogeneity between RCTs. If the P value of the Q test was <0.05 or of I^2 was more than 50%, a random-effects model was used, whereas if the P value of the Q test was >0.05 or I^2 was less than 50%, a fixed-effects model was used. I^2 less than 25% indicated no heterogeneity, 25% to 50% indicated moderate heterogeneity, and greater than 50% indicated severe heterogeneity. If there was heterogeneity in the results, a leave-one-out sensitivity analysis was used to evaluate the stability of the results. P values of <0.05 indicated that the test of group differences had statistical significance. As the total number of studies was less than 10, a funnel plot evaluation for publication bias was not performed because the test power was too low to distinguish chance from real asymmetry (20).

Trial sequential analysis (TSA)

TSA software (beta version 0.9.5.10) was performed to quantify the statistical reliability of outcomes adjusting the significance levels for sparse data. TSA provides the

required information size (RIS) and controls the risks of type I errors due to systematic bias in order to help to clarify whether additional trials are needed. If the cumulative Z-curve crosses the monitoring threshold, the result of the trials is conclusive. According to boundary type, the two-sided option was selected. The risk of type I error was set at 5% with a power of 80%.

Results

Selection of eligible studies

A total of 1,470 citations were obtained from a systematic search. First, 118 duplicate records were removed, and then, 1,273 records were excluded on the basis of title and abstract screening. After reviewing full-text articles, of the remaining 79 studies, a total of 71 studies were excluded based on several criteria. These included the presence of obstructive coronary artery disease (n=29), absence of an assessment mechanism for coronary microvascular function (n=31), and the use of a non-RCT design (n=9). Furthermore, the studies by Birkeland *et al.* (21) and Rambarat *et al.* (22) were considered as substudies of the trial by Bairey Merz *et al.* (19) and were thus also excluded (n=2). Additionally, in our study selection process, we observed that the principal investigators of two RCTs (18,19) were associated with the same medical institution. However, upon thorough scrutiny of the inclusion and exclusion criteria, the duration of ranolazine treatment and the specific methodologies and timelines of each study, we ascertained that these trials were independently conducted with distinct objectives and designs. Accordingly, we deemed it appropriate to include both studies in our meta-analysis, thereby ensuring a comprehensive and rigorous examination of the available literature. Consequently, eight RCTs (18,19,23-28) were eligible for the meta-analysis (*Figure 1*).

Study characteristics

In total, 379 participants were enrolled in these eight studies. The general features of each study are shown in *Table 1*. The proportion of female patients varied widely, ranging from 7% to 100%. The median follow-up duration under treatment was 4 weeks. Across the included studies, in addition to ranolazine therapy, patients received other concomitant anti-ischemic medicines (β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and short- or long-acting nitrates). Coronary microvascular function indicators included CFR, fractional flow reserve (FFR), hyperemic myocardial resistance (HMR), and in some studies, MPRI. All studies provided information on the effects of ranolazine on CFR as evaluated by invasive or noninvasive assessments. Invasive assessments included intracoronary Doppler flow wire (n=3), and noninvasive technologies included transthoracic Doppler echocardiography (n=3) and positron emission tomography–computed tomography (PET-CT) (n=2). However, 2 studies (18,19) did not provide the CFR value. Only one study (28) provided the value of FFR and HMR, in which there were no significant changes in coronary physiology parameters, including FFR and HMR, between any of the groups delineated (P>0.05). In addition, the MPRI was measured by coronary magnetic resonance (CMR) imaging in three studies (18,19,22), including one of the substudies by Bairey Merz *et al.* (19).

Quality of studies

The quality assessment of 8 RCTs is presented in Figure S1. All included studies mentioned randomized grouping. Three of the studies were considered to have a low risk of bias because they specified the use of computerized or online randomization (23,25,28). Other studies had an unclear risk of bias because they did not define their randomization methods. Allocation concealment was considered to carry an unclear risk of bias in all studies because the concealment methods were insufficiently described. Three studies (19,25,26) specified the number of participants who withdrew consent and dropped out midtrial, and the risk of attrition bias was indicated as low in those studies.

Effects of ranolazine on CFR and MPRI

In comparison with the control treatment, ranolazine was associated with no significant differences in the improvement of CFR among patients followed up for 2 to 12 weeks (SMD =0.40; 95% CI: −0.10 to 0.90; P=0.12; chi-squared heterogeneity =17.23; I^2=71%; $P_{heterogeneity}$=0.004) (*Figure 2A*). After the sensitivity analysis (Figure S2), when the trial by Tagliamonte *et al.* (24) was removed, no heterogeneity was detected in the five remaining trials (chi-squared heterogeneity =2.59; I^2=0%; $P_{heterogeneity}$=0.63), and the five studies still revealed no significant differences in the improvement of CFR (SMD =0.14; 95% CI: −0.15 to 0.44; P=0.34) (Figure S3). However, we subsequently conducted

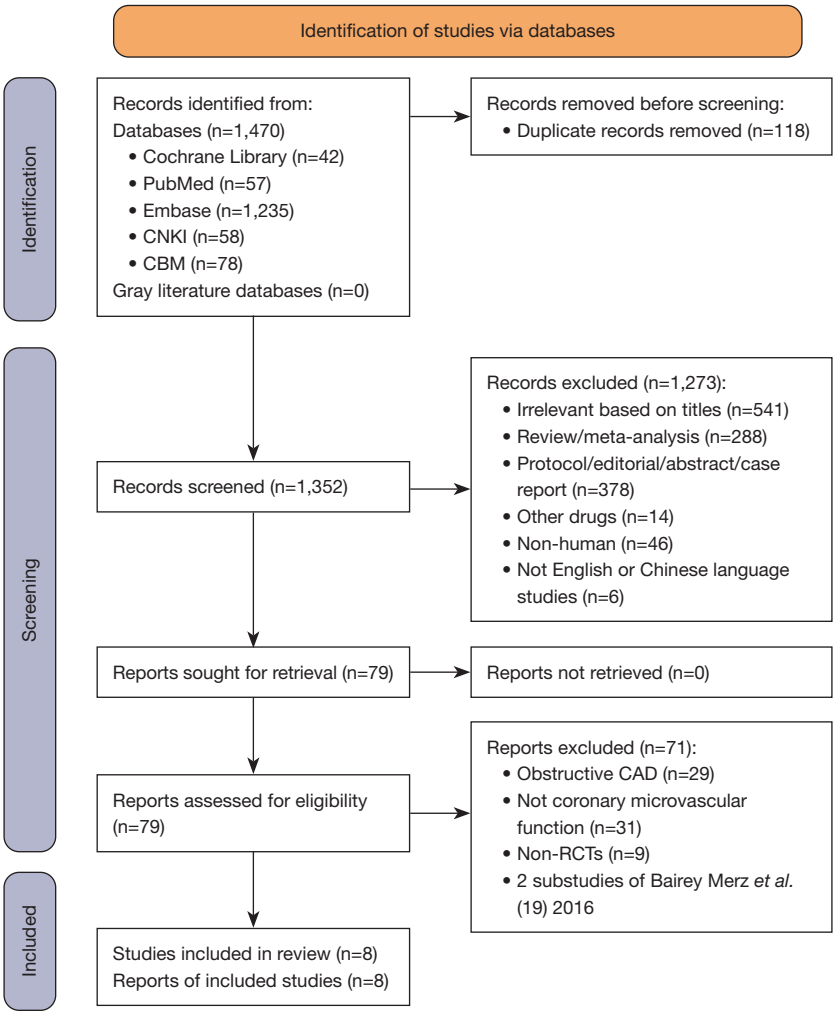

Figure 1 The PRISMA flow diagram of detailed study search and selection process. CNKI, China National Knowledge Infrastructure; CBM, Chinese BioMedical Literature Database; RCT, randomized controlled trial; CAD, coronary artery disease.

a subgroup analysis to determine the cause of heterogeneity and the effect of ranolazine on CFR. It was noted that ranolazine was associated with a significant improvement in CFR after 8 to 12 weeks (SMD =1.16; 95% CI: 0.42–1.89; P=0.002; chi-squared heterogeneity =1.56; I^2=36%; $P_{heterogeneity}$=0.21) (*Figure 2B*). No significant differences in CFR were observed in the dose-dependent subgroups (*Figure 2C*), either in the 500-mg subgroup (SMD =0.06; 95% CI: −0.45 to 0.56; P=0.83; chi-squared heterogeneity =0.00; I^2=0%; $P_{heterogeneity}$=0.96) or in the 500 to 1,000-mg subgroup (SMD =0.69; 95% CI: −0.04 to 1.41; P=0.06; chi-squared heterogeneity =13.45; I^2=78%; $P_{heterogeneity}$=0.004). Sensitivity testing showed that the RCT by Shah *et al.* (26) might have been the potential source of heterogeneity in the high-dose subgroup (Figure S4). After this study was excluded, there was low heterogeneity in the 500- to 1,000-mg subgroup (chi-squared heterogeneity =2.71; I^2=26%; $P_{heterogeneity}$=0.26). The results revealed a significant difference in CFR in the ranolazine-treated group (SMD =1.04; 95% CI: 0.52–1.56; P<0.0001) (Figure S5). TSA provided important information on the trial sequential monitoring boundaries. The TSA of CFR among patients followed up for 2 to 12 weeks in *Figure 3* shows that the cumulative Z-curve did not cross or even reach the RIS [646] or TSA boundary value, which suggests that the current clinical effects of ranolazine in the improvement of CFR among individuals with nonobstructive coronary artery disease need to be confirmed by more trials. In comparison

Table 1 Main features of eight RCTs included in the meta-analysis

First author and year of publication	Study design	Age (year), mean ± SD	Participants, n [% females]	Weeks	Ranolazine dose and follow-up weeks	Method for coronary microvascular function test	Relevant adverse effects
Mehta *et al.* (18)	RCT, double-blind	57.0±11.0	20 [100]	4	500 mg twice daily in 2 weeks and 1,000 mg twice daily in an additional 2 weeks	CFR was measured by Doppler flow-wire, and MPRI was measured by CMRI	Not clear
Bairey Merz *et al.* (19)	RCT, double-blind	55.2±9.8	153 [96]	2	500 mg twice daily in first week and 1,000 mg twice daily in second week	CFR was measured by Doppler flow-wire, and MPRI was measured by CMRI	①②④⑤⑥⑦⑧⑨⑩⑮
Villano *et al.* (23)	RCT, double-blind	58.5±10.0	46 [80]	4	375 mg twice daily in 4 weeks	CFR-ADO and CFR-CPT were measured by transthoracic Doppler echocardiography	No side effects related to the treatment
Tagliamonte *et al.* (24)	RCT, double-blind	65.5±10.5	58 [33]	8	350 mg twice daily in 4 weeks and 500 mg twice daily in an additional 4 weeks	Noninvasive assessment CFR was measured by transthoracic Doppler echocardiography	①②③
Safdar *et al.* (25)	RCT, double-blind	50.0±5.7	31 [71]	4	500 mg twice daily in 1 week and 1,000 mg twice daily in 3 weeks	CFR was measured by PET-CT	①③⑤⑬⑭
Shah *et al.* (26)	RCT, double-blind	64.0±4.6	35 [49]	4	500 mg twice daily in 1 week and 1,000 mg twice daily in 3 weeks	CFR was measured by PET-CT	①⑤⑧⑪⑫
Golino *et al.* (27)	RCT, single-blind	67.3±5.4	15 [7]	3	375 mg twice daily in 3 weeks	CFR-ADO and CFR-CPT were measured by transthoracic echo-color Doppler	Not clear
Koh *et al.* (28)	RCT, double-blind	53.3±12.9	21 [76]	12	500 mg twice daily in 2 weeks and 1,000 mg twice daily in 10 weeks	CFR, FFR, and HMR were measured by Doppler flow velocity guidewire	Not clear

RCT, randomized controlled trial; SD, standard deviation; CFR, coronary flow reserve; CFR-ADO, coronary flow response to adenosine; CFR-CPT, coronary flow response to cold pressor test; MPRI, myocardial perfusion reserve index; CMRI, cardiac magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography; FFR, fractional flow reserve; HMR, hyperemic myocardial resistance; ① gastrointestinal effects (nausea); ② shortness of breath or bronchospasm; ③ palpitations; ④ chest pain; ⑤ dizziness; ⑥ arm shaking; ⑦ back pain; ⑧ renal abnormality; ⑨ throat swelling; ⑩ rectocele; ⑪ hypoglycemia; ⑫ transaminitis; ⑬ constipation; ⑭ headache; ⑮ syncope.

with the control treatment, ranolazine improved the global MPRI (baseline global MPRI <2 or CFR <2.5) (WMD =0.18; 95% CI: 0.07–0.29; P=0.002; chi-squared heterogeneity =0.30; I^2=0%; $P_{heterogeneity}$=0.58) (*Figure 4A*) and the midsubendocardial MPRI (WMD =0.10; 95% CI: 0.02–0.19; P=0.02; chi-squared heterogeneity =1.93; I^2=48%; $P_{heterogeneity}$=0.16) (*Figure 4B*).

Effects of ranolazine on SAQ scores

In comparison with the control group, ranolazine improved 3 of the 5 SAQ scores, namely, physical functioning (WMD =4.89; 95% CI: 0.14–9.64; P=0.04; chi-squared heterogeneity =12.47; I^2=68%; $P_{heterogeneity}$=0.01) (*Figure 5A*), angina stability (WMD =17.31; 95% CI: 7.13–27.49; P=0.0009; chi-squared heterogeneity =21.34; I^2=81%; $P_{heterogeneity}$=0.0003) (*Figure 5B*), and quality of life (WMD =10.11; 95% CI: 3.57–16.65; P=0.002; chi-squared heterogeneity =18.94; I^2=84%; $P_{heterogeneity}$=0.0003) (*Figure 5C*). However, ranolazine did not significantly improve angina frequency (WMD =7.11; 95% CI: 0.10–14.12; P=0.05; chi-squared heterogeneity =13.28; I^2=70%; $P_{heterogeneity}$=0.01) (*Figure 5D*) or treatment satisfaction (WMD =1.38; 95% CI: −4.96 to 7.73; P=0.67; chi-squared heterogeneity =22.57; I^2=82%; $P_{heterogeneity}$=0.0002) (*Figure 5E*). Sensitivity testing did not show the cause of heterogeneity in the physical

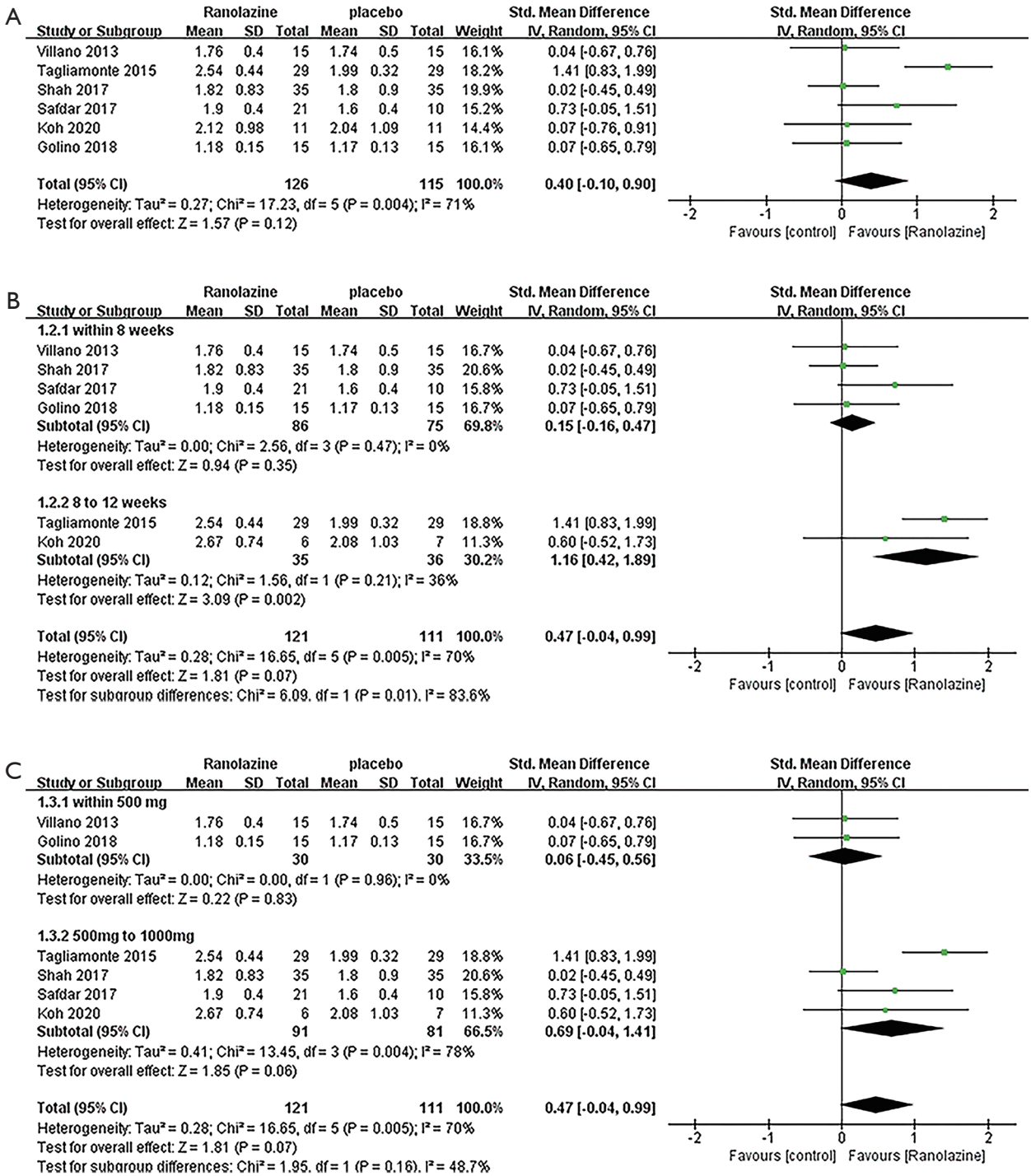

Figure 2 Forest plot of outcomes of CFR. (A) CFR among patients followed up for 2 to 12 weeks. (B) CFR according to follow-up period subgroups. (C) CFR according to subgroups of dose variability. Std, standardized; SD, standard deviation; CI, confidence interval; IV, inverse variance; CFR, coronary flow reserve.

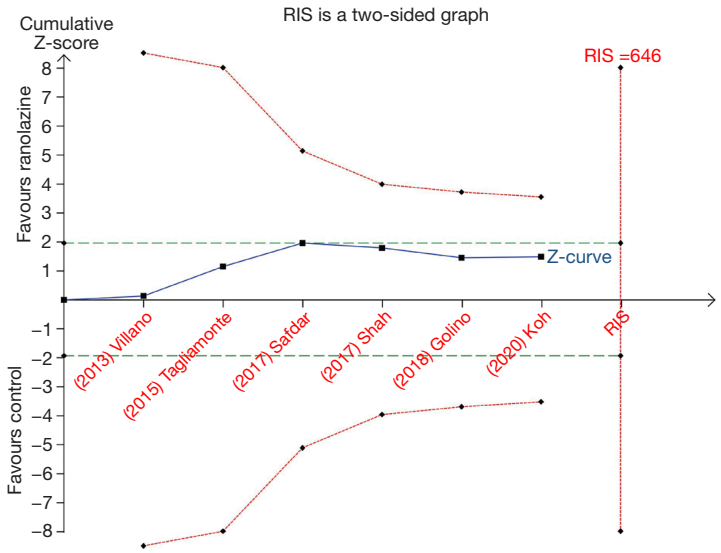

Figure 3 TSA of outcomes of CFR among patients followed up for 2 to 12 weeks. The blue line indicates the cumulative Z score. The horizontal green dashed lines indicate the conventional boundaries. Sloping red lines indicate the trial sequential monitoring boundaries. RIS, required information size; TSA, trial sequential analysis; CFR, coronary flow reserve.

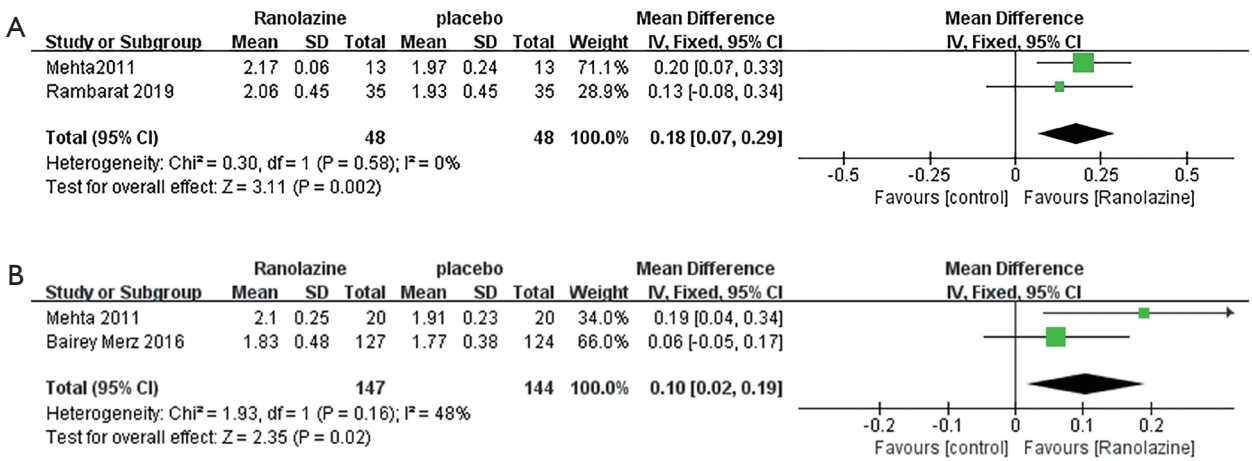

Figure 4 Forest plot of outcomes of the MPRI. (A) Change in the global MPRI (baseline global MPRI <2 or CFR <2.5). (B) Change in the midsubendocardial MPRI. SD, standard deviation; IV, inverse variance; CI, confidence interval; MPRI, myocardial perfusion reserve index; CFR, coronary flow reserve.

functioning score (Figure S6), whereas for the angina stability score, the study by Bairey Merz *et al.* (19) was identified as the potential source of heterogeneity (Figure S7). After this study was removed, there remained high heterogeneity (chi-squared heterogeneity =9.71; I^2=69%; $P_{heterogeneity}$=0.02), and there was still a significant difference in the angina stability score in the ranolazine-treated group (WMD =21.01; 95% CI: 10.60–31.41; P<0.0001) (Figure S8). Moreover, sensitivity testing did not identify the source of heterogeneity in the quality of life score (Figure S9). Additionally, subgroup analysis revealed that the duration of ranolazine intervention exhibited heterogeneity in the quality of life score (chi-squared heterogeneity =13.63; I^2=85.3%; P=0.001). It was noted that ranolazine improved the quality of life score after 8 weeks (WMD =14.70; 95% CI: 10.90–18.50; P<0.00001) (Figure S10), suggesting that the duration was not the cause

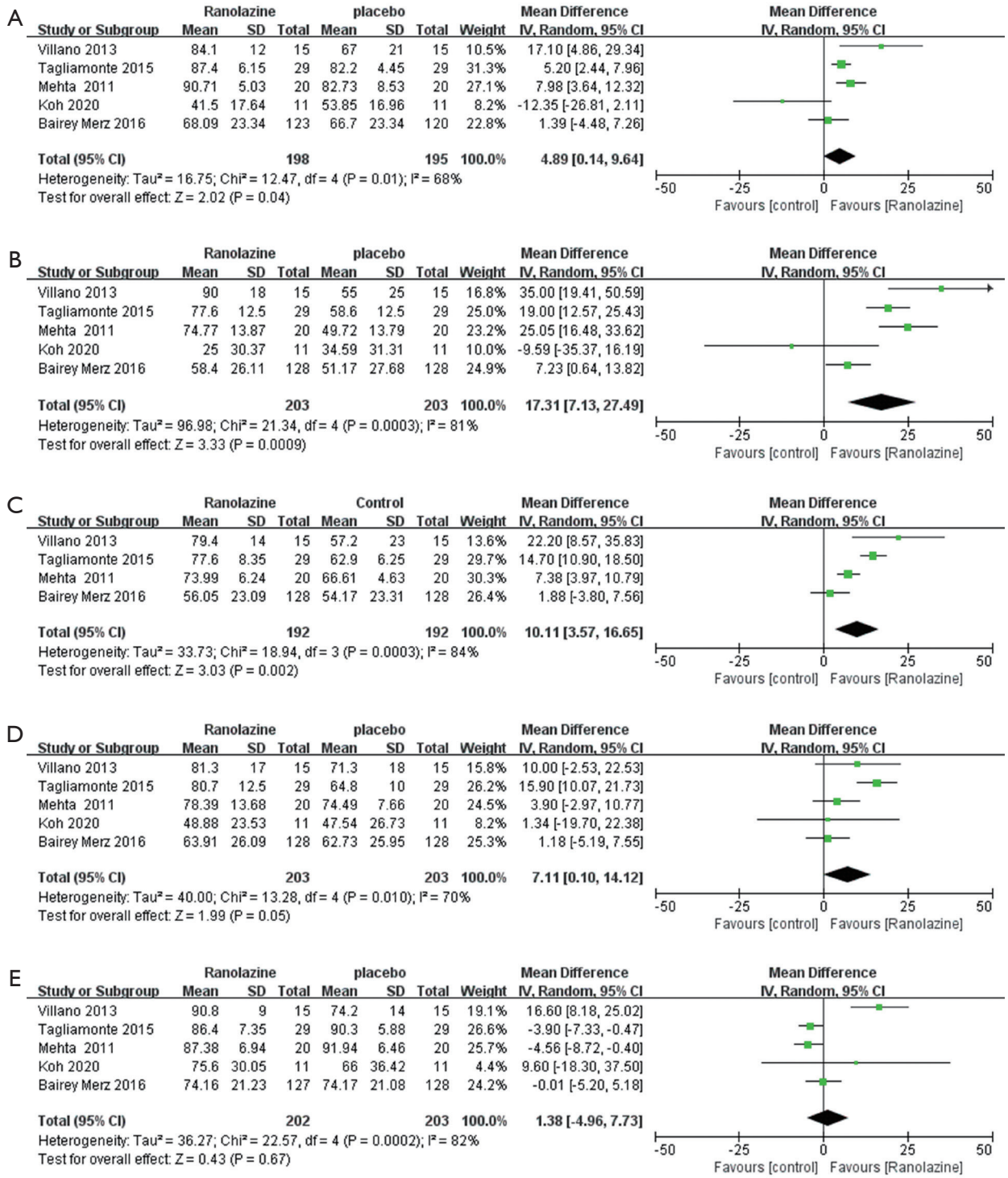

Figure 5 Forest plot of outcomes of Seattle Angina Questionnaire scores. (A) Physical functioning score. (B) Angina stability score. (C) Quality of life score. (D) Angina frequency score. (E) Treatment satisfaction score. SD, standard deviation; CI, confidence interval; IV, inverse variance.

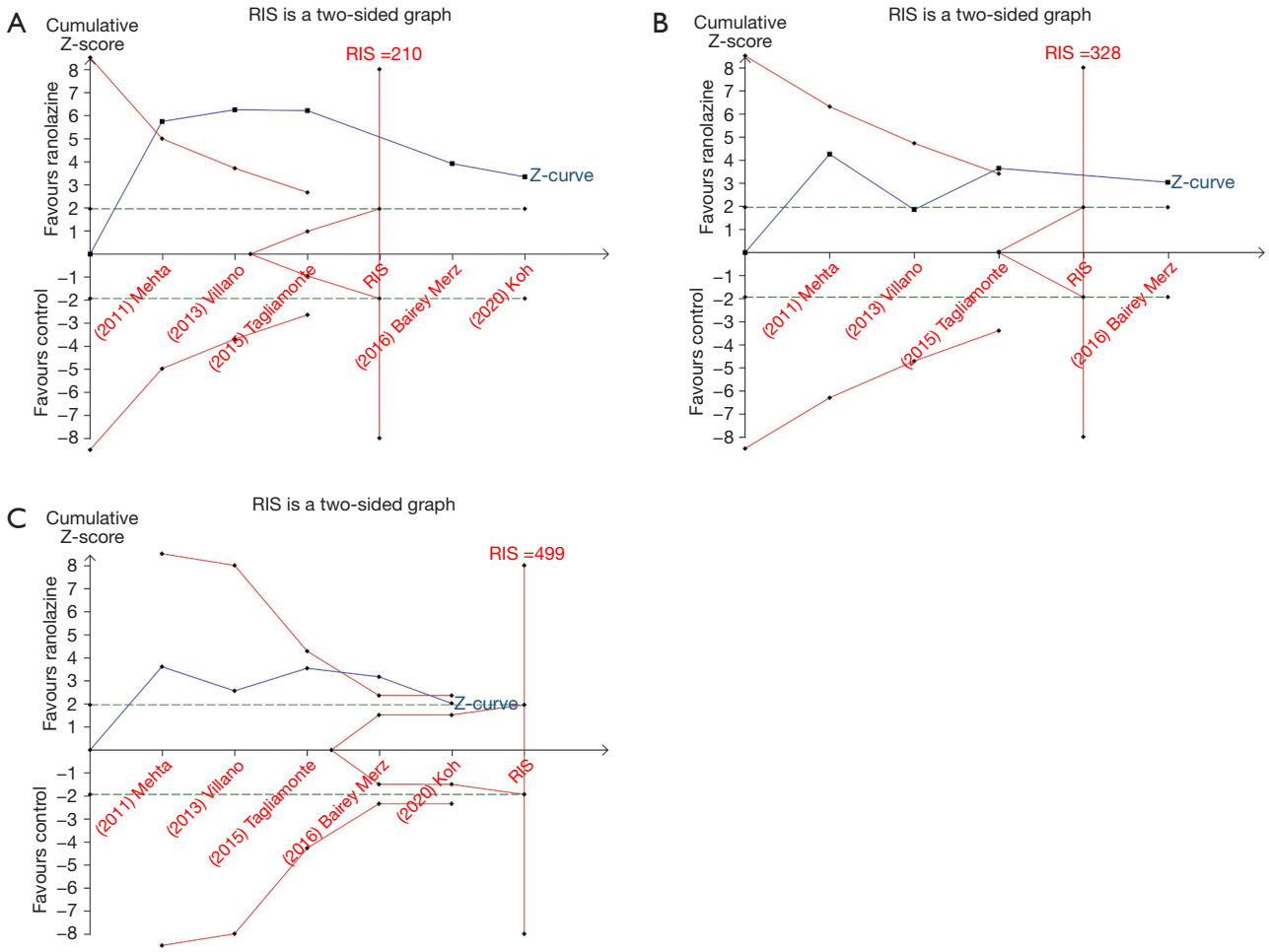

Figure 6 TSA of outcomes of the Seattle Angina Questionnaire scores. (A) TSA of the angina stability score. (B) TSA of the quality of life score. (C) TSA of the physical functioning score. The blue line indicates the cumulative Z score. The horizontal green dashed lines indicate the conventional boundaries. The sloping red lines indicate the trial sequential monitoring boundaries. RIS, required information size; TSA, trial sequential analysis.

of heterogeneity in the subgroup analysis and that ranolazine may improve the quality of life score after 8 weeks. In the TSA results for angina stability and quality of life scores shown in *Figure 6A,6B*, the cumulative Z-curve crosses the RIS threshold (RIS =210 and 328, respectively) and TSA boundary value, suggesting that the existing clinical data on ranolazine in the improvement of these two outcomes are sufficient and conclusive. In the TSA result of the physical functioning score shown in *Figure 6C*, the cumulative Z-curve crosses both the TSA boundary value and the conventional boundary, although the sample size did not exceed the RIS [499]; thus, the result of this meta-analysis is reliable evidence for the efficacy of ranolazine, but the expected values were not attained.

Discussion

In this meta-analysis, we evaluated the effects of the antianginal drug ranolazine on individuals with nonobstructive coronary artery disease. Our analysis revealed that although there were no significant results in the improvement of CFR among individuals who were followed up for 2 to 12 weeks, more trials are needed to confirm this conclusion. In the CFR subgroups, ranolazine was associated with improvement in patients followed up for 8 to 12 weeks. No significant differences in CFR were observed in the dose-dependent subgroups. Additionally, ranolazine improved the MPRI and the SAQ scores for physical functioning, angina stability, and quality of life.

The Coronary Vasomotion Disorders International Study Group (COVADIS) (29) established the clinical criteria for suspicion of microvascular angina and an evidence base to provide guidance in this continually growing patient population. The diagnosis and management of microvascular angina in these individuals with angina and unobstructed coronary arteries are still major challenges compared to the same tasks in patients with conventional angina. Ranolazine is a well-tolerated antianginal medication more recently used as a second-line drug for microvascular angina (30). It is a potent and selective inhibitor that blocks the late sodium channels and reduces calcium influx (31,32), decreasing frequency-dependent diastolic tension and improving coronary blood flow (33). This distinct mechanism represents an alternative therapeutic method for ischemia with nonobstructive coronary arteries (INOCA), differing from conventional antianginal drugs and potentially suiting patients who cannot tolerate these drugs (34). However, additional clinical evidence is needed to confirm these effects.

The impact of ranolazine on coronary microcirculatory function remains a subject of debate in evidence-based medicine. Meta-analyses offer mixed perspectives, some asserting no improvement in CFR with ranolazine and others suggesting significant enhancements (14-16). Key differences lie in the application of fixed-effects or random-effects models, contingent on data heterogeneity. Our study, examining data from RCTs, undertook TSA to evaluate ranolazine's effect on CFR over a 2- to 12-week follow-up period. The TSA results indicated the necessity for additional prospective clinical studies given the substantial risk of false negatives. Notably, despite the high heterogeneity in CFR studies, previous meta-analyses did not conduct subgroup analyses based on follow-up duration or dose variability. Our data suggest ranolazine is associated with the improvement of CFR in patients with an 8- to 12-week follow-up. In the context of long-term angina treatment, ranolazine may demonstrate selective efficacy in individuals with compromised microvascular function. In particular, patients with severe baseline microvascular dysfunction and impaired CFR demonstrated notable improvement. Ranolazine appears to exert benefits mediated by the coronary vasodilatory effect observed in this cohort, a phenomenon that has also been reported in patients with diabetes (35,36). Our meta-analysis also indicates that the current ranolazine dosing regimens may not be optimal for INOCA. Further clinical studies must explore the effects of various doses and durations of ranolazine treatment, specifically for homogenous cohorts (e.g., patients with diabetes, postpercutaneous coronary intervention patients) with severe endothelial dysfunction.

Aside from CFR, the effects of ranolazine on other coronary microvascular functions [e.g., the index of microcirculatory resistance (IMR) and HMR] are crucial because they influence both the pressure and the flow of blood in the coronary microcirculation. One non-RCT study by Ahmed *et al.* (37) showed that ranolazine decreases IMR, which offers an advantage over CFR by excluding the impact of resting hemodynamics and measuring distal pressure at the microvascular level. Koh *et al.* (28) used invasive coronary hemodynamic testing (HMR measurement) to assess the effect of ranolazine in individuals with nonobstructive coronary artery disease; the change in coronary physiology was similar between the placebo and ranolazine groups. Further studies must evaluate the effects of ranolazine on INOCA more comprehensively.

Moreover, using MPRI may help to identify the diffuse hypoperfusion caused by microvascular dysfunction. Thomson *et al.* (38) observed a reduction in MPRI among women with extensive invasive coronary reactivity testing abnormalities. One of our major findings is that ranolazine improves MPRI in patients with a lower baseline global MPRI (<2) or CFR (<2.5), which is consistent with prior meta-analysis findings (15), suggesting that ranolazine may substantially improve MPRI in nonobstructive coronary artery disease populations with more severe CMD. In addition, our meta-analysis showed that ranolazine increased midsubendocardial MPRI, with moderate heterogeneity. Midsubendocardial MPRI reflects a more localized perfusion pattern when responding to microcirculatory change in patients with microvascular angina and may be less affected by epicardial stenosis than may global MPRI (22,39).

In line with several studies, our meta-analysis found improvement in at least one domain of the SAQ in patients taking ranolazine along with other antianginal drugs, adhering to the guidelines that recommend ranolazine as a secondary treatment when first-line drugs are ineffective, contraindicated, or poorly tolerated (8,15,16). This improvement was observed in three out of five SAQ subscales. Notably, a more recent included that was included (28) demonstrated statistical heterogeneity with lower SAQ scores, potentially due to the innovative use of cardiopulmonary exercise testing to evaluate microvascular ischemia. Our subgroup analysis suggests ranolazine may enhance the quality of life score after 8 weeks of treatment. Further, two retrospective studies (40,41) with long-

term follow-ups (1.9 years and 17 months, respectively) demonstrated significant improvement in anginal symptom control and various SAQ domains, supporting ranolazine as an effective treatment option for patients with microvascular angina and refractory angina pectoris. In parallel, enhanced external counterpulsation (EECP) has gained traction in recent years for alleviating clinical symptoms in patients with refractory angina pectoris and enhancing cardiac function in patients with heart failure deemed unsuitable for revascularization procedures (42,43). As an adjunct to pharmacological therapy, EECP fosters the development of coronary collateral vessels, boosting CFR in patients with refractory angina (44,45). Importantly, EECP has been shown to significantly improve patients' quality of life, with sustained benefits noted in clinical follow-ups ranging from 3 months to 2 years posttreatment (46,47). This underscores the potential for multimodal treatment strategies incorporating both ranolazine and EECP to enhance symptom management and quality of life in patients with refractory angina.

The limitations of this meta-analysis should be acknowledged. While our results suggest potential benefits of ranolazine on CFR, MPRI, and SAQ scores, the interpretation of these findings should be tempered with consideration to the small sample sizes and short follow-up periods in some of the included studies. A significant challenge in this field is the heterogeneity of patient cohorts, particularly within the context of multifaceted CMD phenotypes. For instance, patients with diabetes and those who have undergone percutaneous coronary intervention may present distinct CMD profiles. Due to the lack of a sufficient number of RCTs providing disaggregated data for these particular patient groups, we could not conduct a subgroup analysis in our study. This underscores a crucial area for future research. Comprehensive clinical trials are needed that examine the effects of ranolazine while taking into account different doses, treatment durations, and CMD phenotypes. Another limitation lies in the methodological heterogeneity across studies, particularly in the techniques used to measure CFR and MPRI, as this could have potentially influenced the outcomes. Lastly, given that the longest follow-up duration in the included studies was only 12 weeks, there is a pressing need for long-term trials. These would help in comprehensively understanding the impacts of ranolazine on major adverse cardiovascular events and recurrent ischemia in patients with nonobstructive coronary artery disease.

Conclusions

Ranolazine was associated with the improvement of CFR in individuals with nonobstructive coronary artery disease over different follow-up periods. In addition, ranolazine increased myocardial perfusion in patients with low baseline global MPRI or CFR and improved the SAQ scores for physical functioning, angina stability, and quality of life. An extended duration of ranolazine treatment may be associated with an increased quality of life score in the SAQ. Long-term ranolazine treatment provides benefits to patients with ischemia and nonobstructive coronary artery disease; however, further data are needed to determine its effect on the incidence of major adverse cardiovascular events.

Acknowledgments

Funding: This work was supported by grants from the Beijing Municipal Natural Science Foundation (grant no. 7212068) and the National Natural Science Foundation of China (grant no. 81900747).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1029/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1029/coif). All authors reported that this work was supported by grants from the Beijing Municipal Natural Science Foundation (grant no. 7212068) and the National Natural Science Foundation of China (grant no. 81900747). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Hwang D, Park SH, Koo BK. Ischemia With Nonobstructive Coronary Artery Disease: Concept, Assessment, and Management. JACC Asia 2023;3:169-84.
2. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J 2020;41:3504-20.
3. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, Manolis AJ, Marzilli M, Rosano GMC, Lopez-Sendon JL. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol 2018;15:120-32.
4. Cattaneo M, Porretta AP, Gallino A. Ranolazine: Drug overview and possible role in primary microvascular angina management. Int J Cardiol 2015;181:376-81.
5. Pavasini R, Camici PG, Crea F, Danchin N, Fox K, Manolis AJ, Marzilli M, Rosano GMC, Lopez-Sendon JL, Pinto F, Balla C, Ferrari R. Anti-anginal drugs: Systematic review and clinical implications. Int J Cardiol 2019;283:55-63.
6. Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol 2008;97:222-6.
7. Perera D, Berry C, Hoole SP, Sinha A, Rahman H, Morris PD, Kharbanda RK, Petraco R, Channon K; UK Coronary Microvascular Dysfunction Working Group. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British Heart Foundation/National Institute for Health Research Partnership. Heart 2022;109:88-95.
8. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
9. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA; Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309-16.
10. Bertero E, Heusch G, Münzel T, Maack C. A pathophysiological compass to personalize antianginal drug treatment. Nat Rev Cardiol 2021;18:838-52.
11. Rayner-Hartley E, Sedlak T. Ranolazine: A Contemporary Review. J Am Heart Assoc 2016;5:e003196.
12. Cheng K, Alhumood K, El Shaer F, De Silva R. The Role of Nicorandil in the Management of Chronic Coronary Syndromes in the Gulf Region. Adv Ther 2021;38:925-48.
13. Badu-Boateng C, Jennings R, Hammersley D. The therapeutic role of ivabradine in heart failure. Ther Adv Chronic Dis 2018;9:199-207.
14. Yong J, Tian J, Yang X, Xing H, He Y, Song X. Effects of Oral Drugs on Coronary Microvascular Function in Patients Without Significant Stenosis of Epicardial Coronary Arteries: A Systematic Review and Meta-Analysis of Coronary Flow Reserve. Front Cardiovasc Med 2020;7:580419.
15. Zhu H, Xu X, Fang X, Zheng J, Zhao Q, Chen T, Huang J. Effects of the Antianginal Drugs Ranolazine, Nicorandil, and Ivabradine on Coronary Microvascular Function in Patients With Nonobstructive Coronary Artery Disease: A Meta-analysis of Randomized Controlled Trials. Clin Ther 2019;41:2137-2152.e12.
16. Kofler T, Hess S, Moccetti F, Pepine CJ, Attinger A, Wolfrum M, Toggweiler S, Kobza R, Cuculi F, Bossard M. Efficacy of Ranolazine for Treatment of Coronary Microvascular Dysfunction-A Systematic Review and Meta-analysis of Randomized Trials. CJC Open 2021;3:101-8.
17. Zhou W, Lee JCY, Leung ST, Lai A, Lee TF, Chiang JB, Cheng YW, Chan HL, Yiu KH, Goh VK, Pennell DJ, Ng MY. Long-Term Prognosis of Patients With Coronary Microvascular Disease Using Stress Perfusion Cardiac Magnetic Resonance. JACC Cardiovasc Imaging 2021;14:602-11.
18. Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, Yang Y, Gill E, Minissian M, Shaw LJ, Slomka PJ, Slivka M, Berman DS, Bairey Merz CN. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging 2011;4:514-22.
19. Bairey Merz CN, Handberg EM, Shufelt CL, Mehta PK,

Minissian MB, Wei J, Thomson LE, Berman DS, Shaw LJ, Petersen JW, Brown GH, Anderson RD, Shuster JJ, Cook-Wiens G, Rogatko A, Pepine CJ. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. Eur Heart J 2016;37:1504-13.
20. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
21. Birkeland K, Khandwalla RM, Kedan I, Shufelt CL, Mehta PK, Minissian MB, Wei J, Handberg EM, Thomson LE, Berman DS, Petersen JW, Anderson RD, Cook-Wiens G, Pepine CJ, Bairey Merz CN. Daily Activity Measured With Wearable Technology as a Novel Measurement of Treatment Effect in Patients With Coronary Microvascular Dysfunction: Substudy of a Randomized Controlled Crossover Trial. JMIR Res Protoc 2017;6:e255.
22. Rambarat CA, Elgendy IY, Handberg EM, Bairey Merz CN, Wei J, Minissian MB, Nelson MD, Thomson LEJ, Berman DS, Shaw LJ, Cook-Wiens G, Pepine CJ. Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction ancillary study. Int J Cardiol 2019;276:8-13.
23. Villano A, Di Franco A, Nerla R, Sestito A, Tarzia P, Lamendola P, Di Monaco A, Sarullo FM, Lanza GA, Crea F. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol 2013;112:8-13.
24. Tagliamonte E, Rigo F, Cirillo T, Astarita C, Quaranta G, Marinelli U, Caruso A, Romano C, Capuano N. Effects of ranolazine on noninvasive coronary flow reserve in patients with myocardial ischemia but without obstructive coronary artery disease. Echocardiography 2015;32:516-21.
25. Safdar B, D'Onofrio G, Dziura J, Russell RR, Johnson C, Sinusas AJ. Ranolazine and Microvascular Angina by PET in the Emergency Department: Results From a Pilot Randomized Controlled Trial. Clin Ther 2017;39:55-63.
26. Shah NR, Cheezum MK, Veeranna V, Horgan SJ, Taqueti VR, Murthy VL, Foster C, Hainer J, Daniels KM, Rivero J, Shah AM, Stone PH, Morrow DA, Steigner ML, Dorbala S, Blankstein R, Di Carli MF. Ranolazine in Symptomatic Diabetic Patients Without Obstructive Coronary Artery Disease: Impact on Microvascular and Diastolic Function. J Am Heart Assoc 2017;6:e005027.
27. Golino M, Spera FR, Manfredonia L, De Vita A, Di Franco A, Lamendola P, Villano A, Melita V, Mencarelli E, Lanza GA, Crea F. Microvascular ischemia in patients with successful percutaneous coronary intervention: effects of ranolazine and isosorbide-5-mononitrate. Eur Rev Med Pharmacol Sci 2018;22:6545-50.
28. Koh JS, Hung OY, Eshtehardi P, Kumar A, Rabah R, Raad M, Kumar S, Chaudhry S, Gupta S, Hosseini H, Brilakis E, Corban M, Sabbak N, Burnett GM, Liu C, Mehta PK, Quyyumi AA, Samady H. Microvascular Assessment of Ranolazine in Non-Obstructive Atherosclerosis: The MARINA Randomized, Double-Blinded, Controlled Pilot Trial. Circ Cardiovasc Interv 2020;13:e008204.
29. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN; . International standardization of diagnostic criteria for microvascular angina. Int J Cardiol 2018;250:16-20.
30. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
31. Saint DA. The cardiac persistent sodium current: an appealing therapeutic target? Br J Pharmacol 2008;153:1133-42.
32. Shryock JC, Belardinelli L. Inhibition of late sodium current to reduce electrical and mechanical dysfunction of ischaemic myocardium. Br J Pharmacol 2008;153:1128-32.
33. Sharp RP, Patatanian E, Sirajuddin R. Use of Ranolazine for the Treatment of Coronary Microvascular Dysfunction. Am J Cardiovasc Drugs 2021;21:513-21.
34. Tamargo J, Lopez-Sendon J. Ranolazine: a better understanding of its pathophysiology and patient profile to guide treatment of chronic stable angina. Future Cardiol 2022;18:235-51.
35. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol 2003;41:1387-93.
36. Nusca A, Bernardini F, Mangiacapra F, Maddaloni E, Melfi R, Ricottini E, Piccirillo F, Manfrini S, Ussia GP, Grigioni F. Ranolazine Improves Glycemic Variability and Endothelial Function in Patients with Diabetes and Chronic Coronary Syndromes: Results from an Experimental Study. J Diabetes Res 2021;2021:4952447.

37. Ahmed B, Mondragon J, Sheldon M, Clegg S. Impact of ranolazine on coronary microvascular dysfunction (MICRO) study. Cardiovasc Revasc Med 2017;18:431-5.
38. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, Gill EB, Johnson BD, Kenkre T, Handberg EM, Li D, Sharif B, Berman DS, Petersen JW, Pepine CJ, Bairey Merz CN. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. Circ Cardiovasc Imaging 2015;8:e002481.
39. Rahman H, Scannell CM, Demir OM, Ryan M, McConkey H, Ellis H, Masci PG, Perera D, Chiribiri A. High-Resolution Cardiac Magnetic Resonance Imaging Techniques for the Identification of Coronary Microvascular Dysfunction. JACC Cardiovasc Imaging 2021;14:978-86.
40. Rayner-Hartley E, Parvand M, Humphries KH, Starovoytov A, Park JE, Sedlak T. Ranolazine for Symptomatic Management of Microvascular Angina. Am J Ther 2020;27:e151-8.
41. Pargaonkar VS, Tremmel JA, Schnittger I, Khandelwal A. Effect of ranolazine on symptom and quality of life in patients with angina in the absence of obstructive coronary artery disease: A case control study. Int J Cardiol 2020;309:8-13.
42. Raza A, Steinberg K, Tartaglia J, Frishman WH, Gupta T. Enhanced External Counterpulsation Therapy: Past, Present, and Future. Cardiol Rev 2017;25:59-67.
43. Rayegani SM, Heidari S, Maleki M, Seyed-Nezhad M, Heidari M, Parhizgar SE, Moradi-Joo M. Safety and effectiveness of enhanced external counterpulsation (EECP) in refractory angina patients: A systematic reviews and meta-analysis. J Cardiovasc Thorac Res 2021;13:265-76.
44. Casey DP, Beck DT, Nichols WW, Conti CR, Choi CY, Khuddus MA, Braith RW. Effects of enhanced external counterpulsation on arterial stiffness and myocardial oxygen demand in patients with chronic angina pectoris. Am J Cardiol 2011;107:1466-72.
45. Luo C, Liu D, Du Z, Barsness GW, Wu X, Hu C, Li Y, Hu X, Zhang Y, Wu G. Short-term effects of enhanced external counterpulsation on transthoracic coronary flow velocity and reserve in patients with coronary slow flow. Int J Cardiol 2012;154:84-5.
46. Jan R, Khan A, Zahid S, Sami A, Owais SM, Khan F, Asjad SJ, Jan MH, Awan ZA. The Effect of Enhanced External Counterpulsation (EECP) on Quality of life in Patient with Coronary Artery Disease not Amenable to PCI or CABG. Cureus 2020;12:e7987.
47. Soran O, Kennard ED, Kfoury AG, Kelsey SF; IEPR Investigators. Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from The International EECP Patient Registry). Am J Cardiol 2006;97:17-20.

Cite this article as: Ling H, Fu S, Xu M, Wang B, Li B, Li Y, Liu X, Zhang X, Wang Q, Li A, Liu M. Ranolazine for improving coronary microvascular function in patients with nonobstructive coronary artery disease: a systematic review and meta-analysis with a trial sequential analysis of randomized controlled trials. Quant Imaging Med Surg 2024;14(2):1451-1465. doi: 10.21037/qims-23-1029

