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Systematic Review/Meta-analysis

Efficacy of Ranolazine for Treatment of Coronary Microvascular Dysfunction—A Systematic Review and Meta-analysis of Randomized Trials

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ABSTRACT

Background: Coronary microvascular dysfunction (CMD) is a common cause of angina and exercise intolerance in patients without obstructive coronary artery disease. The efficacy of ranolazine, a late sodium channel blocker, in patients with symptomatic obstructive coronary artery disease is well established. To evaluate the efficacy of ranolazine in CMD, we performed a systematic review and meta-analysis of randomized studies.

Methods: MEDLINE, EMBASE, Cochrane CENTRAL, and conference abstracts were searched from January 1975 to March 2020. Randomized trials evaluating ranolazine in patients with CMD were

RÉSUMÉ

Contexte : La dysfonction microvasculaire coronaire (DMC) est une cause courante d'angine et d'intolérance à l'effort chez les patients sans coronaropathie obstructive. L'efficacité de la ranolazine, un bloqueur des canaux sodiques tardifs, chez les patients atteints d'une coronaropathie obstructive symptomatique est bien établie. Pour évaluer l'efficacité de la ranolazine dans le traitement de la DMC, nous avons effectué une revue systématique et méta-analyse d'études à répartition aléatoire.

Méthodologie : MEDLINE, EMBASE, Cochrane CENTRAL et les résumés de congrès ont fait l'objet d'une recherche pour la période allant de

Angina in the absence of a hemodynamically significant stenosis is a conundrum that physicians frequently encounter in their daily practice. With the widespread use of imaging modalities allowing the exact definition of the coronary anatomy (eg, coronary computed tomography or angiography), anginal equivalents and myocardial ischemia in the absence of obstructive coronary artery disease (CAD), with reduced hyperemic myocardial blood flow and thus impaired coronary flow reserve (CFR), referred to as coronary microvascular dysfunction (CMD) or ischemic heart disease without obstructed coronary arteries (INOCA), represent a growing clinical entity. Impaired vasodilation of the coronary microvasculature, microvasculature spasm and extravascular compressive forces have been recognized as important pathophysiologic factors for this form of ischemic heart disease.[1] CMD has also been shown to be associated with an increased risk of adverse cardiovascular events, including myocardial infarction (MI), heart failure–related hospital admissions, and cardiac death.[2] Moreover, a strong female predominance for CMD exists.[3]

Despite improved diagnostics, CMD still represents a challenge in terms of management for involved health care providers.[4,5] A large portion of patients with CMD may have persistent symptoms and an impaired quality of life despite treatment with traditional antianginal drugs, including beta-blockers, calcium channel blockers, or long-acting nitrates.[1] Therefore, several newer drugs with different mechanisms of action have lately been evaluated for symptom control in this patient cohort.[1]

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Ethics Statement: No formal ethics approval was needed to conduct this systematic review and meta-analyis. This systematic review and meta-analysis was elaborated in agreement with the latest version of Cochrane Handbook for Systematic Reviews and Interventions and reported following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement for meta-analysis in healthcare interventions. There was no external funding in place to support this work. The authors are solely responsible for the design and execution of this systematic review and meta-analysis, all analyses, the drafting and editing of the paper, and its final content. Additionally, no individual or organization not listed as an author contributed under any circumstances to the drafting or editing of this manuscript or performance of any analyses presented therein.

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screened. Two reviewers independently extracted data and assessed study quality. End points of interest included a change in angina measured by the Seattle Angina Questionnaire (SAQ), coronary flow reserve (CFR), and clinical outcomes. Data were combined using random-effects models.

Results: Of 836 citations, 6 randomized studies (318 patients) were included. Median follow-up was 4 weeks. When pooling the 6 trials analyzing ranolazine, we found that patients treated with ranolazine had a higher SAQ value regarding physical functioning (mean difference, 6.42; 95% confidence interval [CI], 2.41; 10.42) quality of life (10.07; 95% CI, 3.4; 16.74), and angina stability (20.14; 95% CI, 10.12; 30.17), as well as improved CFR (0.27; 95% CI, 0.09; 0.45) compared with placebo/control therapy. A high heterogeneity was observed (range I^2, 30%-84%).

Conclusions: In CMD, ranolazine may be associated with improvements in CFR and some of the SAQ domains, including angina stability, physical functioning, and quality of life. However, it does not seem to beneficially impact angina frequency and treatment satisfaction. It is also unknown if it improves prognosis of afflicted patients.

janvier 1975 à mars 2020. Les essais à répartition aléatoire sur l'emploi de la ranolazine chez des patients atteints de DMC ont été criblés. Deux examinateurs ont, de manière indépendante, extrait les données et évalué la qualité des études. Les paramètres d'intérêt étaient une variation de l'angine mesurée à l'aide du questionnaire SAQ (*Seattle Angina Questionnaire*), la réserve coronaire et les issues cliniques. Les données ont été combinées avec des modèles à effets aléatoires.

Résultats : Parmi 836 références, six études à répartition aléatoire (318 patients) ont été retenues. La durée médiane de suivi était de quatre semaines. Après avoir regroupé les données des six essais sur la ranolazine, nous avons constaté que les patients traités par la ranolazine avaient un score SAQ plus élevé en ce qui a trait au fonctionnement physique (différence moyenne : 6,42; intervalle de confiance [IC] à 95 % : 2,41 à 10,42), à la qualité de vie (10,07; IC à 95 % : 3,4 à 16,74) et à la stabilité de l'angine (20,14; IC à 95 % : 10,12 à 30,17), de même qu'une réserve coronaire améliorée (0,27; IC à 95 % : 0,09 à 0,45) comparativement aux patients ayant reçu un placebo/traitement témoin. Une forte hétérogénéité a été observée (plage des I^2 : 30 à 84 %).

Conclusions : Dans les cas de DMC, la ranolazine est associée à des améliorations de la réserve coronaire et de certains des domaines du questionnaire SAQ, dont la stabilité de l'angine, le fonctionnement physique et la qualité de vie. Toutefois, elle ne semble pas avoir d'effet bénéfique sur la fréquence de l'angine et la satisfaction à l'égard du traitement. On ne sait pas non plus si elle améliore le pronostic des patients touchés.

Ranolazine is an antianginal drug that inhibits the late sodium current in cardiomyocytes under ischemic conditions.[6] It reduces the intracellular sodium and calcium overload, which in turn improves myocardial relaxation and diastolic function. This ultimately also enhances myocardial contractility and perfusion. Ranolazine is approved for treatment of patients with obstructive CAD. Several studies have lately evaluated the value of ranolazine in patients with CMD, showing some inconsistencies in terms of its magnitude and direction of the effect.[7-13] Therefore, we conducted a systematic review and meta-analysis including all randomized trials assessing the efficacy of ranolazine in patients with CMD.

Methods

This systematic review and meta-analysis was conducted in agreement with the Cochrane Handbook for Systematic Reviews and Interventions and reported following the preferred reporting items for systematic reviews and meta-analyses statement for meta-analysis in health care interventions.[14,15] For reviewing process and data selection, we followed an internal protocol.

Study selection

Because information deriving from observational studies is more susceptible to bias, we only screened randomized studies for eligibility. We comprehensively searched for all randomized clinical trials (RCTs) evaluating the efficacy of ranolazine vs placebo or standard therapy (no ranolazine) in patients with CMD. Case series and studies that were not randomized or did not report clinical outcomes were excluded. Of note, the identified randomized crossover trials were assessed for suitability, as suggested by Cochrane Handbook for Systematic Reviews of Interventions.[16]

In general, CMD was defined as ischemic heart disease in the absence of obstructed coronary arteries: no coronary artery stenosis $>$ 50%-70% or coronary lesions with a fractional flow reserve value $<$0.8, if available.[5,7-12] Of note, only 1 study enrolled patients with coronary artery stenosis up to 70%.[9] In the included studies, cardiac ischemia was assessed by (1) exercise stress-testing,[10] (2) cardiac magnetic resonance tomography,[7,8] or (3) nuclear imaging modalities (single photon emission computed tomography or positron emission tomography/computed tomography).[12] CMD-relevant impairment of CFR was determined as $<$ 2.5.

Two independent reviewers (T.K. and S.H.) reviewed all titles and abstracts for eligibility. Reviewers then assessed full articles for inclusion. Incongruences in assessment were resolved through discussion and consensus involving a third-party opinion (M.B.). Unpublished citations would have also been considered to address negative publication bias.

Data sources

We comprehensively searched for matching RCTs in MEDLINE/PUBMED, Cochrane CENTRAL Register of Controlled Trials, and EMBASE published any time since January 1, 1975. Our search process was completed by March 2, 2020. Any article published after that date was not included. In addition, we manually searched the abstracts submitted to the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and Transcatheter Therapeutics up to March 2, 2020. The ClinicalTrials.gov registry and results database for clinical

studies was searched for ongoing or recently finished trials. We carefully reviewed the reference lists of original studies identified by the electronic search to ensure that all pertinent studies were included. We used the search terms "ranolazine," "cardiac syndrome X," "late sodium channel blocker," "coronary microvascular dysfunction," "CMD," "ischemic heart disease without obstructed coronary arteries," and "INOCA." The detailed search terms are listed in Supplemental Table S1. To ensure data completeness, we contacted the included study's corresponding author, if necessary.

Data collection and quality assessment

Two reviewers (T.K. and S.H.) extracted the data independently using the Covidence software package (Melbourne, VIC, Australia). Any disagreements were resolved by consensus. Residual uncertainty was clarified with the senior author (MB). The Kappa (κ) statistic, calculated to assess the degree of agreement between the 2 authors ($\kappa = 0.89$), indicates a substantial agreement. The quality of the studies was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool for randomized trials (Supplemental Table S2).[16] In case of incomplete data, the authors were directly contacted by e-mail, at least 2 times if necessary, in order to pool their data.[5]

Outcomes

We obtained the outcomes for the longest available follow-up. The following outcomes were evaluated: (1) symptoms and physical functioning assessed by the Seattle Angina Questionnaire (SAQ), which is a well-validated, self-administered, disease-specific, questionnaire assessing 5 dimensions related to ischemic heart disease, including physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception;[17,18] (2) the Duke Activity Status Index, which is established for estimation of functional capacity;[19] (3) any adverse reactions to the study drugs; and (4) the influence of ranolazine administration on cardiac function and perfusion (eg, CFR, assessed by echocardiography, cardiac magnetic resonance tomography, and positron emission tomography).[7-10,12]

Statistical analysis

We assessed outcomes based on clinical and methodological heterogeneity to determine whether pooling was appropriate. Point estimates are presented as the mean difference. Heterogeneity was estimated using the I^2 statistics with P-values.[14] Because heterogeneity was large (based on $I^2 >$ 25%), we used random-effects models to assess mean differences between continuous variables; data are reported in mean differences and standard error (SE) with 95% confidence intervals (CIs). Publication bias was assessed by visual analysis of funnel plots. The included trials were evaluated for risk of bias in 5 domains (sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and incomplete outcome data) according to the risk of bias tool from the Cochrane collaboration.[14,20,21]

We defined *a priori* a sensitivity analysis of high-quality studies for each clinical outcome. Of note, limited patient number and missing data impaired conduction of meaningful subgroup analyses. We used Review Manager software version 5.3 (Rev Man, The Nordic Cochrane Centre, Copenhagen, Denmark) for the statistical analyses. A P-value < 0.05 was considered statistically significant.

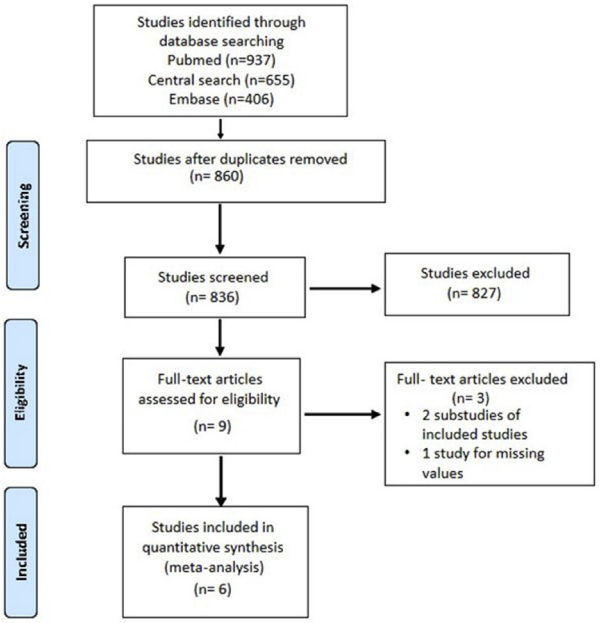

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram detailing the article screening of the review.

Results

As displayed in Figure 1, 836 citations were identified, of which 9 were selected for full review;[5,7-13,22] 6 RCTs comparing ranolazine vs placebo/standard therapy (no ranolazine) in patients with CMD fulfilled the eligibility criteria and were ultimately selected for the exploratory analyses.[7-12] The inverted funnel plot for the end point overall SAQ did not suggest any significant publication bias (Supplemental Fig. S1).

Included studies

Characteristics of the trials included in the meta-analysis are presented in Tables 1 and 2. The 6 selected RCTs included 318 patients, whereas 239 (75%) were females and the mean age was 57.5 ± 5.9 years. The median follow-up duration under treatment was 4 weeks. The concomitant anti-ischemic medication varied across the included studies; as an example in the ranolazine group, 132 patients (41.5%) were taking β-blockers. Four studies provided information on the impact of ranolazine on coronary flow over time as assessed by cardiac imaging.[9,10,12,23]

Effects of ranolazine on SAQ score and other health questionnaires

The symptomatic effect of ranolazine is highlighted in the forest plots in Figure 2. The included studies suggested higher SAQ scores regarding physical functioning, quality of life, and angina stability in the ranolazine group. However, there was no significant difference in the SAQ score regarding angina frequency and treatment satisfaction. Publication bias was limited by the small number of studies included (n = 6). Two

Table 1. Summary of the included studies

Study	Year of study	Study location/sites	Design	Comparison	Outcomes	Mean treatment duration (wk)
Mehta et al.[7]	2011	USA, single centre	Randomized, double blind, placebo-controlled crossover trial	Ranolazine (500-1000 mg BID) vs placebo	(1) SAQ score; (2) DASI; (3) percentage of ischemic myocardium and MPRI	4
Villano et al.[8]	2013	Italy, single centre	Randomized, double blind, placebo-controlled trial	Ranolazine (375 mg BID) vs ivabradine (5 mg BID) vs placebo BID	(1) SAQ score; (2) EuroQoL scale; (3) exercise stress test; (4) FMD/NMD; (5) CFR (assessed by transthoracic Doppler echocardiography)	4
Tagliamonte et al.[9]	2015	Italy, single centre	Randomized, double blind, placebo-controlled trial	Ranolazine (500 mg BID) vs placebo BID	(1) SAQ score; (2) CFR (assessed by transthoracic Doppler echocardiography); (3) left ventricular systolic fraction assessed by echocardiography	8
Bairey Merz et al.[10]	2016	USA, multicentre	Randomized, double-blind, placebo-controlled, crossover trial	Ranolazine (500-1000 mg) vs placebo BID	(1) SAQ score; (2) angina diary, DASI, and general quality of life (QoL); (3) stress MPRI assessed by CMR; (4) diastolic filling assessed by CMR.	2
Safdar et al.[23]	2017	USA, single centre	Randomized, double blind trial	Ranolazine (500-1000 mg) BID vs placebo	(1) CFR assessed by attenuation corrected PET imaging	4
Shah et al.[12]	2017	USA, single centre	Randomized, double-blind, placebo-controlled, crossover trial	Ranolazine (500-1000 mg) vs placebo BID	(1) CFR assessed by attenuation corrected PET imaging	4

BID, twice a day; CFR, coronary arterial flow reserve; CMR, cardiac magnetic resonance tomography; DASI, Duke Activity Status Index; EuroQoL, European quality of life visual analog scale; FMD, peripheral flow–mediated dilation; MPRI, quantitative myocardial perfusion reserve index; NMD, nitrate-mediated dilatation; PET, positron emission tomography; SAQ, Seattle Angina Questionnaire.

studies assessed the Duke Activity Status Index (DASI) and did not indicate any significant difference (Supplemental Fig. S2A). The study conducted by Villano et al. highlighted that ranolazine compared with placebo significantly improved the European quality of life visual analog scale (79.3 ± 13 vs 64.3 ± 19, $P < 0.0001$).[8]

Effects of ranolazine on CFR

The effects of ranolazine on CFR are highlighted in Figure 3. The mean baseline CFR of the 4 analyzed studies was 1.93. Those patients receiving ranolazine appeared to have a significant improvement in CFR. Two studies assessed the myocardial perfusion index and did not show a significant difference between the 2 groups (Supplemental Fig. S2A).[8,10]

Safety outcomes

Contraindications and known adverse drug reaction under ranolazine are listed in Table 3. One study reported 5 adverse events (1 bronchospasm, 1 hospitalization for non-ST-segment MI, 2 presyncopes, and 1 syncope).[7] Mehta et al. also mentioned 2 cases of gastrointestinal side effects.[7] Minor adverse effects, which were reported in totally 11 patients, included nausea, diarrhoea, dizziness, hypoglycemia, rise in creatinine, and transaminitis.[12,24] No other serious adverse events had been reported.

Discussion

In our systematic review and meta-analysis, we evaluated the efficacy of ranolazine in patients with CMD. Overall, we found that late sodium current blockade using ranolazine did improve angina stability, quality of life, and physical functioning. Notably, patients with CMD with a reduced CFR at baseline (< 2.5) appear to have a more pronounced benefit from ranolazine therapy. However, ranolazine did not show any consistent improvement in the myocardial perfusion reserve index, diastolic filling, or angina frequency and treatment satisfaction.

To understand the relevance of our meta-analysis, one needs to take in account that evidence-based and effective therapies for CMD are still limited. So far, disease-modifying therapies that have been suggested to provide benefit comprise statins and angiotensin-converting enzyme inhibitors.[25] In terms of symptom management, the latest guidelines recommend beta-blockers as first-line therapy and calcium antagonists, if the former are not tolerated or efficacious in afflicted patients. Interestingly, there is evidence that long-acting nitrates are ineffective or even detrimental in microvascular disease.[4] In this context, ranolazine had lately been promoted as a possible therapeutic option for CMD, because it has been shown to improve diastolic and endothelial function.[26,27]

Ranolazine has been recommended for the treatment of selected patients with chronic angina in obstructive CAD who have persistent symptoms despite optimal medical treatment (including β-blockers or calcium channel blockers).[6] Earlier studies of ranolazine have been conducted in patients with confirmed CAD and ischemic ST-segment changes during treadmill testing (before completion of 9 minutes on a modified Bruce protocol)[28,29] or with at least 3 episodes of angina per week despite taking calcium channel blockers. These trials confirmed that ranolazine increases the time to ischemia on treadmill testing, improves exercise duration, and

Table 2. Baseline characteristics of patients in the included studies

Study	Patients, n (% females)	Mean age (y)	Mean BMI (kg/m^2)	Family Hx of premature CAD, n (%)	Hypertension, n (%)	Dyslipidemia, n (%)	Smoking,* n (%)	Diabetes, n (%)	Concomitant anti-ischemic therapy		
									β-Blockers, n (%)	Nitrates, n (%)	Ca channel blockers, n (%)
Mehta et al.[7]	20 (100)	57	25.6	14 (70)	10 (50)	12 (60)	10 (50)	N/A	14 (70)	9 (45)	4 (20)
Villano et al.[8]	46 (80)	58	27	12 (80)	13 (87)	8 (53)	2 (13)	N/A	31 (67)	5 (11)	21 (46)
Tagliamonte et al.[9]	58 (33)	65	26.4	6 (21)	19 (65)	15 (52)	8 (28)	7 (24)	55 (95)	N/A	N/A
Bairey Merz et al.[10]	128 (96)	55	29.3	83 (65)	69 (54)	70 (55)	40 (31)	23 (18)	54 (42)	50 (39)	29 (23)
Safdar et al.[23]	31 (65)	49	30	4 (40)	4 (40)	4 (40)	4 (40)	5 (24)	6 (19)	1 (3)	7 (23)
Shah et al.[12]	35 (49)	64	31	11 (31)	30 (86)	33 (94)	2 (6)	13 (37)	22 (63)	7 (20)	9 (26)

BMI, body mass index; CAD, coronary artery disease; Hx, history; N/A, not available.
* Includes current and former smoking.

limits the frequency of angina in highly symptomatic patients.[10]

In the randomized, double-blind, placebo-controlled, MERLIN-TIMI 36 trial, which enrolled 6560 patients presenting with non-ST-segment MI, ranolazine compared with placebo did not significantly reduce the primary end point, including cardiovascular death, MI, or recurrent ischemia (21.8% vs 23.5%; hazard ratio, 0.92; 95% CI, 0.83-1.02). However, the secondary end point recurrent ischemia itself was significantly reduced in patients receiving ranolazine compared with placebo (13.9% vs 16.1%; hazard ratio, 0.87; 95% CI, 0.76-0.99; $P = 0.03$). In addition, ranolazine appeared to be safe and did not increase the risk for death from any cause or symptomatic arrhythmias.[29]

Regarding the treatment satisfaction and angina frequency (as assessed by SAQ) with ranolazine, we have to state that there was no difference compared with placebo/standard therapy. Whether this is related to polymedication due to the additional pill or due to other not assessed factors remains uncertain. However, ranolazine appeared to be generally well tolerated and very few patients required dose adjustments or treatment discontinuation of ranolazine due to side effects. Interestingly, no patient had to discontinue ranolazine for prolongation of the QT interval, which is recommended to be monitored while taking this drug (see Table 3).

Regarding patient selection for ranolazine in CMD, data from the Women's Ischemic Syndrome Evaluation investigators might be informative. Their study also suggested that patients with a reduced baseline CFR (< 2.5) were most likely to benefit from ranolazine, with significant improvements in myocardial perfusion ($P = 0.014$) and angina frequency ($P = 0.027$).[5] This has also recently been indicated by a comprehensive meta-analysis of Zhu et al.,[30] which implicated an enhanced efficacy of ranolazine in CMD subgroups with a baseline CFR < 2.5 or a global quantitative myocardial perfusion reserve index < 2.

In contrast, ranolazine is unlikely to be beneficial in patients with CMD triggered by enhanced susceptibility to vasoconstrictive stimuli, who represent a considerable proportion, or in those whose symptoms are predominantly caused by a hypersensitive heart syndrome.[31]

Among the included studies, Tagliamonte et al.[9] found the most consistent benefit from ranolazine in terms of SAQ improvement. This could be explained by the fact that their study had the longest mean follow-up (8 weeks). In contrast to patients with relevant CAD, patients with CMD might need longer treatment duration to benefit optimally from ranolazine. On the basis of current data, it is supposed that prolonged treatment duration is required for relevant improvement of diastolic function.[25,32] Therefore, the lack of longer-term data could be the explanation for the missing effect of ranolazine on angina frequency and treatment satisfaction in our study.

Overall, our analysis highlights that there is a need for more dedicated trials assessing currently used therapies in patients with CMD. Also, more research is necessary to understand the mechanisms of microvascular ischemia to identify novel treatment targets. So far, our meta-analysis suggests a potential benefit of ranolazine in highly symptomatic patients with CMD with reduced CFR, namely by improving

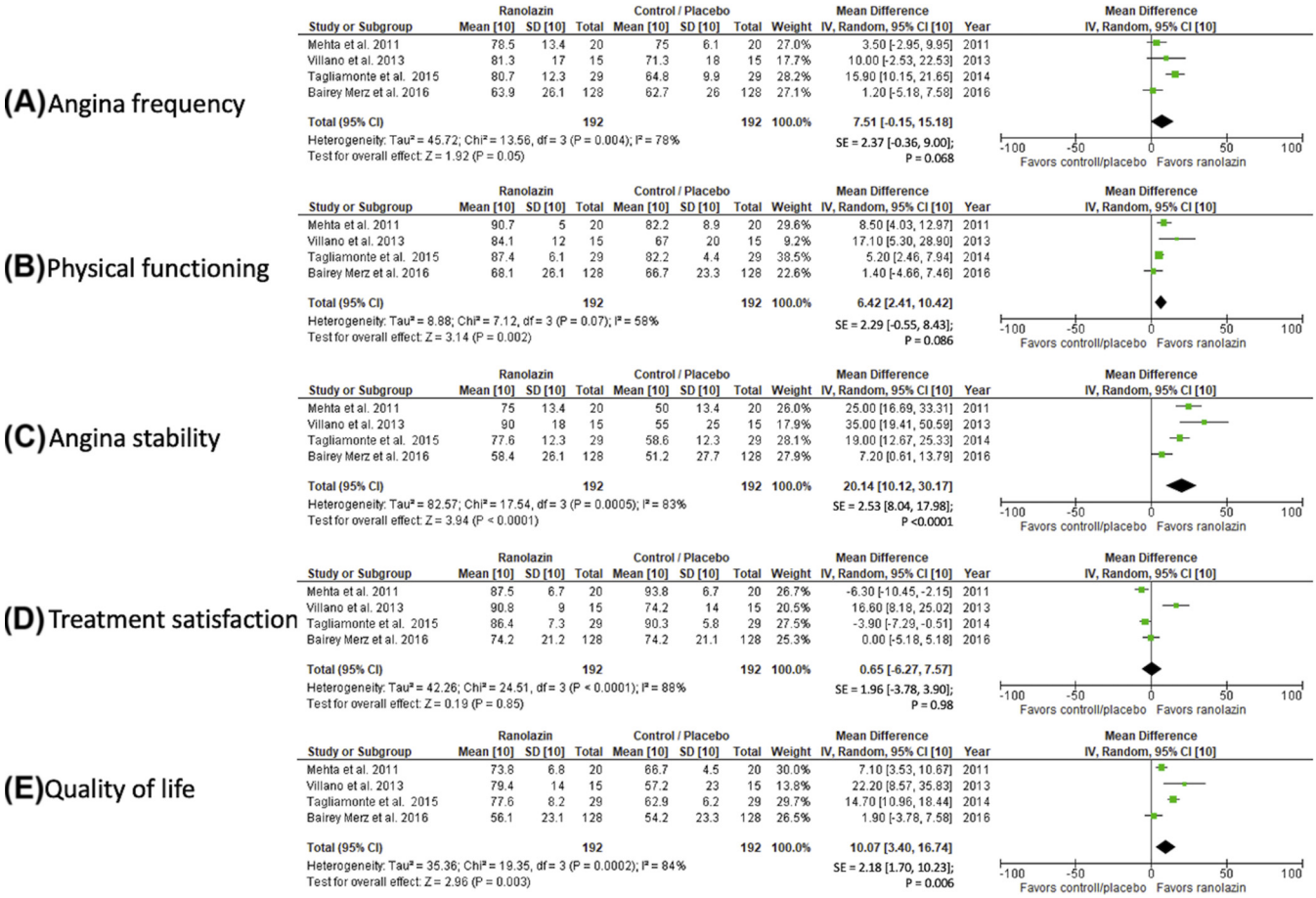

Figure 2. Impact of ranolazine vs placebo on angina equivalents in patients with coronary microvascular dysfunction: (**A**) angina frequency; (**B**) physical functioning; (**C**) angina stability; (**D**) treatment satisfaction; and (**E**) quality of life. CI, confidence interval; IV, weighted mean difference; SE, standard error; SD, standard deviation.

angina symptoms, quality of life, and physical functioning. Furthermore, the use of ranolazine in CMD appears to be safe. However, potential contraindications need to be considered and side effects (Table 3) monitored regularly.

Limitations

We are well aware of several limitations applying to our meta-analysis. First, the small sample size as well as the short follow-up period influenced some analyses. On one hand, it impaired conducting appropriate meta-regression analyses to establish possible associations between the summary effects and the study-level data.[33] On the other hand, the dataset did not allow us to assess the effect of ranolazine on major cardiovascular events. Second, it is important to annotate that a significant number of patients enrolled in the meta-analyzed studies did in fact not have typical angina. Third, the crossover design of most studies bears several limitations. Although this study design can be suitable in the context of assessing the efficacy of a drug for treatment of CMD, some carryover effects (despite applying a washout period) may occur. Furthermore, this design can be subject to period

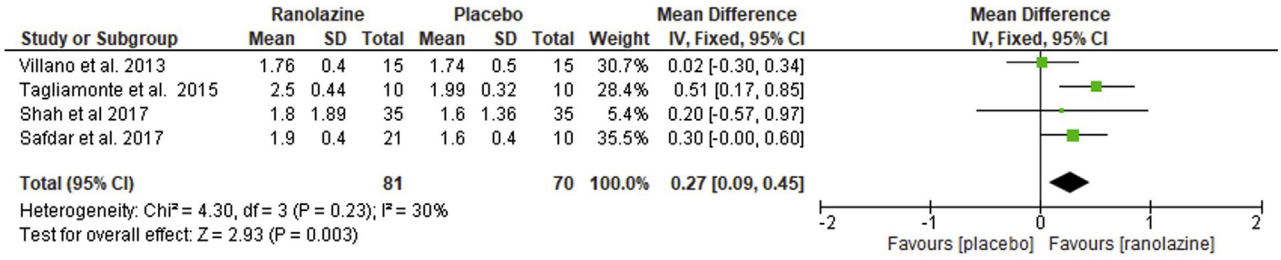

Figure 3. Change in coronary flow reserve with ranolazine vs placebo in patients with microvascular dysfunction. CI, confidence interval; IV, weighted mean difference; SD, standard deviation.

Table 3. Contraindications and relevant adverse effects of ranolazine

(A) Contraindications	
• Severe renal insufficiency (GFR < 30 mL/min)	
• Moderate or severe liver insufficiency	
• Medication with CYP3A4 inhibitors	
• Medication with class IA and class II antiarrhythmic drugs	
(B) Possible side effects	
Endocrine system	≥ 1/1000, < 1/100: anorexia, dehydration, loss of weight
	< 1/1000: hyponatremia
Metabolism and kidneys	≥ 1/1000, < 1/100: dysuria, hematuria, rise in serum creatinine
GI-/hepatic system	≥ 1/100, < 1/10: obstipation, nausea
Cardiovascular system	≥ 1/1000, < 1/100: prolonged QTc interval
Nervous system	≥ 1/100, < 1/10: headache, vertigo
Integument	≥ 1/1000, < 1/100; prurigo, hyperhidrosis
Skeletal-/muscle system	≥ 1/1000, < 1/100: muscle pain, muscle weakness, joint swelling
Blood-/immune system	≥ 1/1000, < 1/100: thrombo- and leukocytosis

GFR, glomerular filtration rate; GI, gastrointestinal.

effects where differences in the effectiveness of an intervention can occur. Fourth, CFR was assessed with different methods in the included studies. Fifth, the assessed heterogeneity between the single studies was high. Thus, the results need to be interpreted very cautiously and firm inferences cannot be drawn due to the limited data. Sixth, the proportion of concomitant anti-ischemic drugs varied across the included studies. For instance, this could have directly impacted myocardial perfusion (eg, quantitative myocardial perfusion reserve index) and therefore also some domains of the SAQ score, including particularly treatment satisfaction, which in turn hampers the meta-analysis somewhat.[10] Finally, the definition of CMD and therefore the patients included showed some variation among the studies, which might additionally influence the results. To the best of our knowledge, this is however one of the first systematic reviews and meta-analyses with an in-depth assessment of the role of ranolazine in patients with CMD.

Conclusions

Among symptomatic patients with CMD, ranolazine seems associated with improvements in CFR and some of the SAQ domains, namely angina stability, physical functioning, and quality of life. However, it does not appear to beneficially impact angina frequency and treatment satisfaction. Overall, these results need to be interpreted with caution and firm inferences may not be drawn due to the data's limitations. It also remains unclear if it has any influence on other clinical outcomes, including rehospitalization for angina and death, in patients with CMD. Accordingly, ranolazine might only be considered for selected symptomatic patients with CMD. Of course, possible contraindications and side effects need to be carefully monitored. There certainly is a need for an adequately powered prospective trial evaluating the long-term safety and efficacy in patients with CMD.

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References

1. Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease. Circulation 2018;138:1463-80.
2. Nishi T, Murai T, Ciccarelli G, et al. Prognostic value of coronary microvascular function measured immediately after percutaneous coronary intervention in stable coronary artery disease: an international multicenter study. Circ Cardiovasc Interv 2019;12:e007889.
3. Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. J Am Coll Cardiol 2017;70:2349-58.
4. Marinescu MA, Loffler AI, Ouellette M, et al. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. JACC Cardiovasc Imaging 2015;8:210-20.
5. Rambarat CA, Elgendy IY, Handberg EM, et al. 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.
6. Rayner-Hartley E, Sedlak T. Ranolazine: a contemporary review. J Am Heart Assoc 2016;5:e003196.
7. Mehta PK, Goykhman P, Thomson LE, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging 2011;4:514-22.
8. Villano A, Di Franco A, Nerla R, et al. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol 2013;112:8-13.
9. Tagliamonte E, Rigo F, Cirillo T, et al. Effects of ranolazine on noninvasive coronary flow reserve in patients with myocardial ischemia but without obstructive coronary artery disease. Echocardiography 2015;32:516-21.
10. Bairey Merz CN, Handberg EM, Shufelt CL, et al. 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.
11. Saha S, Ete T, Kapoor M, et al. Effect of ranolazine in patients with chest pain and normal coronaries—a hospital based study. J Clin Diagn Res 2017;11:Oc14-O16.
12. Shah NR, Cheezum MK, Veeranna V, et al. Ranolazine in symptomatic diabetic patients without obstructive coronary artery disease: Impact on microvascular and diastolic function. J Am Heart Assoc 2017;6:e005027.
13. Ahmed B, Mondragon J, Sheldon M, Clegg S. Impact of ranolazine on coronary microvascular dysfunction (MICRO) study. Cardiovasc Revasc Med 2017;18:431-5.

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

16. (updated September 2020) In: Higgins JPT, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.1. *Cochrane*, 2020. Available from: www.training.cochrane.org/handbook.

17. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.

18. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. Circulation 2002;106:43-9.

19. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651-4.

20. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

21. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

22. Birkeland K, Khandwalla RM, Kedan I, et al. 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.

23. Safdar B, D'Onofrio G, Dziura J, et al. Ranolazine and microvascular angina by PET in the emergency department: results from a pilot randomized controlled trial. Clin Ther 2017;39:55-63.

24. Cattaneo M, Porretta AP, Gallino A. Ranolazine: drug overview and possible role in primary microvascular angina management. Int J Cardiol 2015;181:376-81.

25. Deshmukh SH, Patel SR, Pinassi E, et al. Ranolazine improves endothelial function in patients with stable coronary artery disease. Coron Artery Dis 2009;20:343-7.

26. Chaitman BR, Pepine CJ, Parker JO, et al. 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.

27. Hwang H, Arcidi JM Jr, Hale SL, et al. Ranolazine as a cardioplegia additive improves recovery of diastolic function in isolated rat hearts. Circulation 2009;120:S16-21.

28. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375-82.

29. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775-83.

30. Zhu H, Xu X, Fang X, et al. 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;41:2137-52. e2112.

31. Nelson MD, Sharif B, Shaw JL, et al. Myocardial tissue deformation is reduced in subjects with coronary microvascular dysfunction but not rescued by treatment with ranolazine. Clin Cardiol 2017;40:300-6.

32. Nash DT, Nash SD. Ranolazine for chronic stable angina. Lancet 2008;372:1335-41.

33. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.

Supplementary Material

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