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 included. Studies were independently assessed for eligibility, and all analyses were performed using a random-effects model. The meta-analysis was performed using RevMan 5.3 software.

Findings: A total of 13 randomized trials evaluating ranolazine in patients with CMD were identified. The pooled analysis showed a significant reduction in angina frequency and duration.

Conclusion: Ranolazine is an effective treatment for CMD.

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...
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.\(^7\) 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.\(^15\) 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.\(^5\) Of note, only 1 study enrolled patients with coronary artery stenosis up to 70%.\(^5\) In the included studies, cardiac ischemia was assessed by (1) exercise stress-testing,\(^10\) (2) cardiac magnetic resonance tomography,\(^7\) or (3) nuclear imaging modalities (single photon emission computed tomography or positron emission tomography/computed tomography).\(^15\) 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 (κ = 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). 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.

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; (2) the Duke Activity Status Index, which is established for estimation of functional capacity; (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).

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 $I^2$ statistic, calculated to assess the degree of heterogeneity 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.

We defined a priori a sensitivity analysis of high-quality studies for each clinical outcome. Of note, limited patient number and missing data impaired conduct 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.

Results

As displayed in Figure 1, 836 citations were identified, of which 9 were selected for full review, 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. 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.

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 | Design | Year of study | Study locations |
|-------|--------|---------------|-----------------|
| Mehta et al.7 | USA, single centre | 2011 | Randomized, double-blind, placebo-controlled crossover trial |
| Villano et al.8 | Italy, single centre | 2013 | Randomized, double-blind, placebo-controlled trial |
| Tagliamonte et al.9 | Italy, single centre | 2015 | Randomized, double-blind, placebo-controlled trial |
| Safdar et al.23 | USA, single centre | 2017 | Randomized, double-blind, placebo-controlled trial |
| Bairey Merz et al.10 | USA, multicentre | 2016 | Randomized, double-blind, placebo-controlled trial |
| Saldar et al.12 | USA, single centre | 2017 | Randomized, double-blind, placebo-controlled trial |

| Outcomes | Mean treatment duration (wk) |
|----------|-----------------------------|
| (1) SAQ score; (2) DASI; (3) end point of ischemic myocardial perfusion reserve index; diastolic filling assessed by CMR; (4) CFR (assessed by transthoracic Doppler echocardiography); (5) left ventricular systolic fraction assessed by echocardiography; (6) DPO/NMD; (7) CMR, cardiac magnetic resonance tomography; (8) DASI, Duke Activity Status Index; (9) EuroQoL scale; (10) FMD/NMD; (11) Saqq, Seattle Angina Questionnaire. |

Ranolazine (500-1000 mg BID) vs placebo
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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. Minor adverse effects, which were reported in totally 11 patients, included nausea, diarrhoea, dizziness, hypoglycemia, rise in creatinine, and transaminis.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.26 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).7 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
limits the frequency of angina in highly symptomatic patients.\textsuperscript{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.\textsuperscript{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 (\( P = 0.027\)).\textsuperscript{5} This has also recently been indicated by a comprehensive meta-analysis of Zhu et al.,\textsuperscript{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.\textsuperscript{31}

Among the included studies, Tagliamonte et al.\textsuperscript{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.\textsuperscript{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

**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 primary CAD, n (% females) | Hypertension, n (% females) | Dyslipidemia, n (% females) | Diabetes, n (% females) | Concomitant anti-ischemic therapy | Smoking, \( ^\ast \), n (% females) |
|-------|-------------------------|--------------|------------------------|----------------------------------------|---------------------------|---------------------------|-------------------------|--------------------------------|----------------------------------|
| Mehta et al.\textsuperscript{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.\textsuperscript{8} | 46 (80) | 58 | 27 | 12 (80) | 13 (87) | 8 (53) | 2 (13) | N/A | 31 (67) | 5 (11) | 21 (46) |
| Tagliamonte et al.\textsuperscript{9} | 58 (33) | 65 | 26.4 | 6 (21) | 8 (28) | 15 (52) | 10 (34) | N/A | 55 (95) | 2 (2.3) | N/A |
| Bairey Merz et al.\textsuperscript{10} | 128 (96) | 55 | 29.3 | 83 (65) | 70 (55) | 40 (31) | 4 (3.1) | 54 (42) | 29 (23) | 7 (5.5) | 6 (4.7) |
| Safdar et al.\textsuperscript{23} | 31 (65) | 49 | 30 | 4 (13) | 4 (13) | 4 (13) | 4 (13) | 55 (95) | 5 (16) | 1 (3) | 7 (23) |
| Shah et al.\textsuperscript{12} | 35 (49) | 64 | 31 | 13 (37) | 22 (63) | 7 (20) | 7 (20) | N/A | 13 (37) | 3 (9) | N/A |

BMI, body mass index; CAD, coronary artery disease; Hx, history; N/A, not available.

\( ^\ast \) Includes current and former smoking.
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. 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 2](image-url). 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.

![Figure 3](image-url). Change in coronary flow reserve with ranolazine vs placebo in patients with microvascular dysfunction. CI, confidence interval; IV, weighted mean difference; SD, standard deviation.
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 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.

### 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.

### Funding Sources

No extramural funding was used to support this work.

### Disclosures

R.K. has received institutional grant support from Abbott, Biotronik, Biosense Webster, Boston, Medtronic, and SIS Medical. M.B. received consulting and speaker fees from Astra Zeneca, Amgen, and Bayer, as well as travel grants from Pfizer and Vifor SA. The rest of the authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.09.005.