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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

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ABSTRACT

Background: In a prior trial of late sodium channel inhibition (ranolazine) among symptomatic subjects without obstructive coronary artery disease (CAD) and limited myocardial perfusion reserve index (MPRI), we observed no improvement in angina or MPRI, overall. Here we describe the clinical characteristics and myocardial perfusion responses of a pre-defined subgroup who had coronary flow reserve (CFR) assessed invasively.
Methods: Symptomatic patients without obstructive CAD and limited MPRI in a randomized, double-blind, crossover trial of ranolazine vs. placebo were subjects of this prespecified substudy. Because we had previously observed that adverse outcomes and beneficial treatment responses occurred in those with lower CFR, patients were subgrouped by CFR <2.5 vs ≥2.5. Symptoms were assessed using the Seattle Angina Questionnaire and the SAQ-7, and left-ventricular volume and MPRI were assessed by magnetic resonance imaging (MRI). Coronary angiograms, CFR, and MRI data were analyzed by core labs masked to treatment and patient characteristics.
Results: During qualifying coronary angiography, 81 patients (mean age 55 years, 98% women) had invasively determined CFR 2.69 ± 0.65 (mean ± SD; range 1.4–5.5); 43% (n = 35) had CFR <2.5. Demographic and symptomatic findings did not differ comparing CFR subgroups. Those with low CFR had improved angina ($p = 0.04$) and midventricular MPRI ($p = 0.03$) with ranolazine vs placebo. Among patients with low CFR, reduced left-ventricular end-diastolic volume predicted a beneficial angina response.
Conclusions: Symptomatic patients with CFR <2.5 and no obstructive CAD had improved angina and myocardial perfusion with ranolazine, supporting the hypothesis that the late sodium channel is important in management of coronary microvascular dysfunction.
Trial registration: clinicaltrials.gov Identifier NCT01342029

1. Introduction

Angina pectoris affects almost 2% of the global population and contributes to poor quality of life and increased healthcare resource consumption [1]. In approximately 60%–70% of symptomatic women and 20%–30% of men referred to angiography to evaluate symptoms and/or signs of ischemia, no flow-limiting coronary stenosis is identified [2]. Despite this high prevalence, multiple studies indicate that among such patients absence of obstructive coronary artery disease (CAD) is not a benign condition as it is associated with heightened risk for adverse outcomes [2–7]. Even with traditional antianginal therapy, management of these patients remains challenging as the reasons for angina and ischemia are often multifactorial and may include coronary microvascular dysfunction (CMD) [8].

In ischemic myocardium, the late inward sodium current contributes to calcium overload with related left ventricular (LV) diastolic dysfunction [9], which has potential to further limit the ability to increase coronary flow. Among patients with symptoms and/or signs of ischemia with

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non-obstructive CAD, diastolic dysfunction by cardiac magnetic resonance imaging (CMRI) [10] as well as echocardiography [11] has been associated with reduced CFR. The late sodium current is inhibited by ranolazine, which improves LV function in experimental models with myocardial ischemia [12] and effort angina in patients with ischemic heart disease (IHD) manifest by CAD that was likely obstructive [13,14]. In preliminary studies of patients with CMD, ranolazine improved angina and coronary flow reserve (CFR), especially among women with reduced CFR [9,15,16].

These preliminary results support the suggestion that inhibition of the late inward sodium current may beneficially impact myocardial blood flow in patients with ischemia related to CMD. However, these prior studies were all small sample size (20 to 58 patients), single-center trials, and a larger, multicenter trial was warranted to address this knowledge gap. Advances in CMRI perfusion [17] conduct a multicenter trial in 128 patients with signs and symptoms of IHD but no obstructive CAD, with reduced myocardial perfusion reserve (MPRI) to test mechanistically whether symptoms are related to reduced MPRI and whether they could be influenced by late sodium current inhibition [18]. We found that late sodium current inhibition with short-term ranolazine exposure did not improve angina, assessed by the Seattle Angina Questionnaire (SAQ) or MPRI.

Accordingly, we investigated the subgroup of patients enrolled in the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction (WISE-CVD) project who also had CFR measured during clinically indicated invasive coronary reactivity testing (CRT) just prior to entry into the ranolazine trial [19]. This report summarizes results of that ancillary study.

2. Methods

2.1. Patient population

Inclusion/exclusion criteria, study protocol, and investigators appear in Supplementary material online [18]. Briefly, we enrolled women and men with signs and symptoms of ischemia, no obstructive CAD (<50% epicardial coronary stenosis in all epicardial coronary arteries determined by core lab), and preserved LV ejection fraction, who had an invasive CRT and evidence for CMD (defined as either a global MPRI <2.0, failure to dilate with acetylcholine, or CFR <2.5). Institutional review boards approved the study at the sites, and all patients gave written informed consent.

2.2. Study design

To mechanistically test effects of late sodium channel inhibition among patients with reduced CFR, we conducted a double-blind, placebo-controlled, crossover trial with ranolazine and placebo exposure order randomly assigned. Angina measured by the SAQ and SAQ-7 were the co-primary outcomes. Other outcomes of interest included stress MPRI, LV diastolic filling, and quality of life (QoL). Absence of obstructive CAD and CRT measures were core-lab ascertained (WISE Angiography and Coronary Reactivity Cores). At baseline and follow-up visits, subjects completed demographic/health history questionnaires, the SAQ and SAQ-7.

Study periods were 2 weeks in duration, followed by 2-week washout, and crossover to 2 weeks of alternate therapy. Ranolazine (Gilead Sciences, Foster City, CA, USA) was administered as 500 mg orally twice daily for 1-week and increased to 1000 mg twice daily for 1 week as tolerated (subjects taking verapamil or diltiazem maintained ranolazine or placebo 500 mg twice daily). Treatment compliance was measured by pill count. Data were collected at baseline (SAQ and SAQ-7) and at the end of each treatment period (SAQ, SAQ-7, and CMRI). Other anti-anginal medications were unchanged during the study.

2.3. Invasive coronary reactivity testing (CRT)

Clinically indicated invasive CRT was performed in 87 subjects to measure coronary micro and macrovascular endothelial and non-endothelial-dependent function, as previously published [7,19], and 81 CFR measurements with complete CMRI and SAQ data. CFR was measured with use of Doppler flow-wire (FloWire Volcano, San Diego, CA, USA) in a proximal left coronary branch (usually the left anterior descending) following intracoronary adenosine injections. All measurements were made in WISE angiographic and CRT core labs masked to treatment period and other patient data.

2.4. Cardiac magnetic resonance imaging (CMRI)

The CMRI protocol (see Supplementary material online, Exhibit B) was performed (1.5 Tesla, Siemens Sonata, Erlangen, Germany) with electrocardiographic gating and phased array coil with 0.05 mmol/kg gadolinium first-pass perfusion (three slice) at rest and during pharmacological stress [20]. This was done with intravenous adenosine (140 μg/kg/min), or regadenoson (0.40 mg) if intolerant, and was consistent within specific subjects for each of their respective study periods. CMRI was conducted under identical conditions and timing, dosing, and settings, 4-h after their morning study drug dose. First-pass perfusion images were analyzed using CMRI analysis software (CAAS MRV Version 3.3, Pie Medical Imaging B.V., Maastricht, Netherlands). Software-determined epicardial and endocardial contours of LV myocardium were manually corrected to make time-intensity curves. Global sub-endocardial and sub-epicardial MPRI were calculated as the ratio of stress/rest relative perfusion upslope. Sub-endocardial and sub-epicardial layers were software determined as the inner and outer 50% wall thickness. These methods have high interstudy and observer reproducibility [21], with best reproducibility in the mid ventricle [22]. LV mass and volumes were evaluated by manual tracing; papillary muscles were included in the LV mass/excluded from the LV volume. Volumetric diastolic filling was used to calculate early peak filling rate and time to peak filling rate [10]. All of these analyses were done in the WISE MRI Core masked to other patient information.

2.5. Sample size considerations and statistical analysis

Subjects were randomized at a 1:1 ratio and blocked by clinical site. With a 2×2 crossover design, a sample size of 80 would achieve 90% power to detect a mean difference of 10 in SAQ angina frequency score using a two-sided *t*-test at the 0.017 Holm-Bonferroni-corrected level of significance, and SD of 24 for a paired difference. The detectable difference in SAQ-7, using a SD of 16 for a paired difference would be 6.84. The detectable difference using a SD of 0.49 for a paired difference in global MPRI, would be 0.205, and for a SD of 0.54 in mid-sub-endocardial MPRI the minimum detectable difference would be 0.226.

Continuous variables are expressed as mean ± SD or % where appropriate. Consistent with prior WISE analyses, a CFR of <2.5 was used to define CMD and patients were subgrouped accordingly. The analytic approach was a within-subject comparison (paired) of the difference between baseline-treatment periods for a total of four measurements per subject. This included two baseline periods and two treatment periods. The distribution of within-subject differences was assessed to deploy appropriate statistical techniques. The primary approach for continuous variables was a standard paired *t*-test. Linear regression models were tested using treatment differences as the outcome. A stepwise procedure was used to choose variables that were significantly associated with outcomes. The overall type I error rate for the three co-primary outcome measures was controlled at 5% by the HB36 sequential procedure. Carryover effects tested the interaction between treatment and period by comparing the mean within subject with means between the arms. Subgroup analyses included relevant clinical variables [23], prior ranolazine exposure, randomization sequence, site, full vs. reduced ranolazine dose, prior myocardial infarction by history or CMRI-late gadolinium enhancement, and qualifying CRT and CMRI variables. The significance level for outcomes other than the three co-primary endpoints was set to 0.05. All subjects included completed the SAQ and SAQ-7 at baseline; SAQ, SAQ-7, and CMRI for both treatment periods; and took ≥50% of drug for both periods. Analyses were performed using SAS v9.3 (SAS Institute, Inc., Cary, NC, USA). A sensitivity analysis excluding male subjects was performed. Coronary artery disease severity scores were calculated on all subjects with available data [24].

2.6. Study oversight

The study was an investigator-initiated ancillary trial to the National Heart, Lung and Blood Institute (NHLBI)-sponsored WISE-CVD, funded in part by Gilead Sciences, with oversight by the WISE Data Safety Monitoring Committee. Statistical analysis was performed by investigators independent of NHLBI and Gilead. The decision to submit for publication was made by the investigators who had access to all data after the last subject completed the study.

3. Results

3.1. Study population

The 81 subjects (mean age 55 years) with invasive CFR testing before the baseline study period had a CFR of 2.69 ± 0.65 mean (±SD); 35 (43.2%) had a CFR <2.5 and 46 (56.8%) had a CFR ≥2.5. Of the 81 subjects, 65 (80%) had data for the extent of coronary artery disease. Ten subjects (11%) had no CAD (0–<20% stenosis) and 55 (89%) had minimal CAD (≥20 to <50% stenosis). Of the 65 subjects, 40 (62%) had CFR ≥2.5 and 25 (38%) had CFR <2.5. Of those 40 with CFR ≥2.5, 37 (93%) had minimal CAD vs 7% with no CAD. Of the 25 with CFR <2.5, 18 (72%) had minimal CAD. There were 62 subjects with CAD severity score data and they ranged from 5 to 22.75 with mean of 10.6 ± 4.3. The mean severity score among the 40 subjects with CFR ≥2.5 was 10.95 ± 4.14, and the mean severity score among the 25 with CFR <2.5 was 9.92 ± 4.7. Thus, over all these were mostly patients with minimal CAD and CFRs ≥2.5, at baseline. There were no significant differences comparing baseline characteristics among these CFR groups (Table 1). The majority

Table 1
Pertinent baseline demographic and clinical variables.

Mean ± SD or absolute frequency (%)	All subjects (n = 81)	CFR <2.5 (n = 35)	CFR ≥2.5 (n = 46)	p-Value
Age (y)	54.77 ± 10.19	54.43 ± 10.80	55.02 ± 9.82	0.80
Female	80 (98.8%)	34 (97.14%)	46 (100%)	0.43
Body mass index	29.62 ± 7.50	28.31 ± 6.70	30.61 ± 7.99	0.17
Race (non-white)	21 (25.9%)	11 (31.43%)	10 (21.74%)	0.44
Current smoking	2 (2.5%)	0	2 (4.35%)	1.0
History of hypertension	40 (49.4%)	16 (45.71%)	24 (52.17%)	0.64
Diabetes mellitus (n = 80)	16 (19.8%)	4 (14.7%)	12 (26.09%)	0.28
History of hyperlipidemia	44 (54.3%)	15 (42.86%)	29 (63.04%)	0.08
Family history of premature CAD	50 (61.7%)	23 (65.71%)	27 (58.70%)	0.35
Postmenopausal (n = 80)	65 (80.2%)	28 (82.35%)	37 (80.43%)	1.0
No CAD (<20% stenosis)	65/81 (80.2%)	7 (28.0%)	3 (7%)	0.44
Minimal CAD (20—<50% stenosis)		18 (72.0%)	37 (93%)	
Prior myocardial infarction	4 (4.9%)	2 (5.71%)	2 (4.35%)	1.0
Typical angina	26 (32.1%)	10 (28.75%)	16 (34.78%)	0.63
Angina frequency (baseline SAQ angina frequency domain)	59.75 ± 27.02	62.29 ± 27.66	57.83 ± 26.66	0.43
LVEDP (mm Hg) (n = 69)	14.55 ± 4.66	14.63 ± 6.01	14.50 ± 3.62	0.60
Beta-blockers	37 (45.7%)	18 (51.43%)	19 (41.30%)	0.38
Calcium channel blocker	20 (24.7%)	5 (14.29%)	15 (32.61%)	0.07
ACEI or ARB	31 (51.8%)	10 (28.57%)	21(47.33%)	0.17
Nitrates	33 (40.7%)	13 (37.14%)	20 (43.48%)	0.65
Statin	48 (59.2%)	17 (48.57%)	31 (67.39%)	0.11
Hormone replacement therapy	12 (14.8%)	5 (14.29%)	7 (15.22%)	1.0

ACEI or ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CAD, coronary artery disease; CFR, coronary flow reserve; LVEDP, left-ventricular end diastolic pressure; SAQ, Seattle Angina Questionnaire; SD, standard deviation.

were women (98.8%), and white subjects comprised about three-quarters of the study patients in both groups and almost half had a history of hypertension. There were no significant differences in use of beta-blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors. Baseline SAQ angina frequency scores were similar between those with CFR <2.5 (62.29 ± 27.66) and those with CFR ≥2.5 (57.83 ± 26.66, p = 0.43). Likewise, their left ventricular end diastolic pressures were not different. The sensitivity analysis excluding the male subject showed no significant change in baseline characteristics and SAQ angina frequency scores.

3.2. Medication compliance

Overall compliance was 91% (74/81 subjects). Among the 81 subjects, 14 (17%) (ranolazine) and 9 (11%) (placebo) were reduced to 500-mg twice-daily dosing due to side effects believed to be medication-associated. Adverse events in the ranolazine subgroup consisted of emergency room visits due to arm shaking, bronchospasm, wheezing, and nausea/lightheadedness. One adverse event, an emergency room visit due to chest pain, occurred in the placebo subgroup. When grouped by CFR, total rate of medication compliance for CFR <2.5 was 98.1% and for CFR ≥2.5 was 97.1%. Compliance with ranolazine in both groups was reduced when compared with placebo (96.5% vs 99.6% for CFR <2.5; 94.6% vs 98.6% for CFR ≥2.5).

3.3. Acetylcholine and CFR assessment

Acetylcholine testing (n = 73) documented endothelial dysfunction (coronary diameter decreased −2.42 ± 20.18, mean ± SD) but there was no difference comparing CFR groups. Impaired CFR was not associated with any specific pattern of response to acetylcholine (r = 0.1, p = 0.39). Among those with CFR <2.5, there was no significant correlation between CFR and acetylcholine response (r = −0.06, p = 0.747).

3.4. Effect of ranolazine on CFR and MPRI

When receiving ranolazine, patients with a CFR of <2.5 had improvement in angina by the SAQ-7 vs placebo (Δ5.76 ± 11.51 vs. Δ-0.86 ± 13.54; CI: 0.28, 12.96) (Fig. 1). Likewise, in patients with CFR of <2.5 there was a significant decrease in the SAQ angina frequency scale with ranolazine vs placebo (Δ9.14 ± 17.55 vs. Δ-0.29 ± 14.24; CI: 1.14, 17.72). Similar changes were not observed in patients with CFR

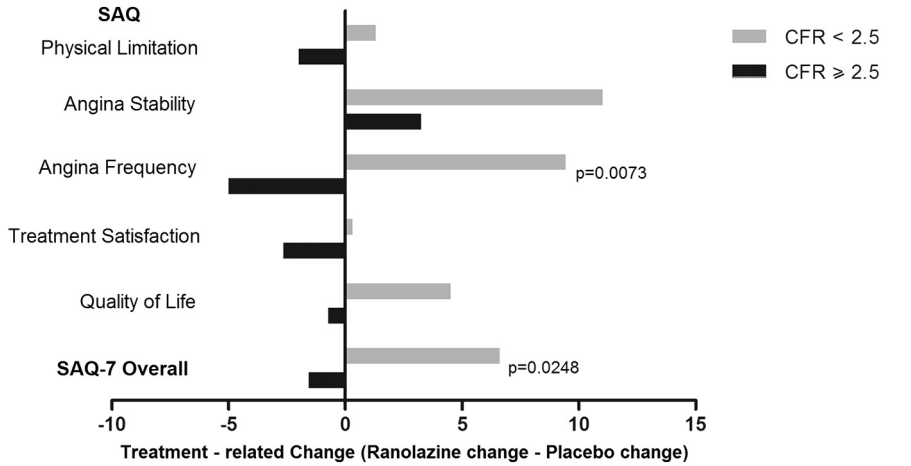

Fig. 1. Mean 2-week change in Seattle Angina Questionnaire (SAQ and SAQ7) score (ranolazine change–placebo change).

≥2.5. Additionally, patients with a CFR <2.5 had improved global MPRI vs a decrease for global MPRI in patients with CFR ≥2.5 (Δ0.12 ± 0.58 for patients with CFR <2.5 and Δ-0.15 ± 0.44 for patients with CFR ≥2.5, *t*-test p = 0.02) (Fig. 2). Change in midventricular MPRI had a similar difference in these subgroups (Δ0.27 ± 0.68 among patients with CFR <2.5, and Δ-0.11 ± 0.5 in patients with CFR ≥2.5, *t*-test p = 0.005) (Fig. 2). There was a direct correlation between change in SAQ-7 scores and MPRI (correlation 0.23; p = 0.04). There was no significant difference in ranolazine effect on MPRI in subjects with CFR < 2.5 who had no CAD vs. minimal CAD (Δ MPRI 0.05 ± 0.53 vs. 0.18 ± 0.52, p = 0.40). The sensitivity analysis excluding the male patient showed no statistically significant change in the effect of ranolazine on SAQ-7, SAQ angina frequency, global MPRI and mid-ventricular MPRI.

In those with CFR <2.5 with ranolazine, global MPRI was higher than the ischemic threshold of 2.0 in 57%, whereas with placebo, global MPRI was >2.0 in 33%. Likewise, for midventricular MPRI, 53% of patients with CFR <2.5 had an MPRI >2.0 with ranolazine whereas only 34% had an MPRI >2.0 with placebo. By comparison, in patients with CFR ≥2.5, global MPRI was >2.0 in 41% with ranolazine and in 54% with placebo. When analyzed by midventricular MPRI, MPRI was >2.0 in 50% of patients receiving ranolazine and 60% of those receiving placebo.

4. Discussion

In this short-term trial of late sodium current inhibition in patients with symptoms/signs of ischemia but no obstructive CAD, those with CFR <2.5 had improvement in SAQ angina frequency and SAQ-7 scores and higher MPRI when receiving ranolazine vs placebo. These results support those of several previous single-center studies, of smaller sample size [9,15,16].

In a prior single-center pilot study of 20 women with mostly typical angina, no obstructive CAD, and ≥10% ischemic myocardium on adenosine stress CMRI, ranolazine improved angina [9]. Additionally, among 13 of the women with invasive CRT, those with a CFR ≤3.0 had significantly improved MPRI when receiving ranolazine compared with placebo (Δ MPRI 0.48 vs −0.82; p = 0.04) [9]. In a second study of 58 patients (19% women) with angina and myocardial ischemia but no obstructive CAD, ranolazine 500 mg twice daily for 8 weeks, compared with placebo, was associated with an increase in transthoracic Doppler echocardiography–derived CFR (2.54 ± 0.44 vs. 1.91 ± 0.31; p = 0.005) and decreased angina symptoms [15]. Symptom improvement was attributed to improved CMD and interestingly, 88% of patients had a baseline CFR <2.5, consistent with our study. In another study of 46 patients with stable angina, abnormal exercise stress tests, no obstructive CAD, and CFR <2.5, ranolazine 375 mg twice daily for 4 weeks was associated with improvement in angina vs placebo [16]. Of note, the study did not detect a change in CFR with adenosine using transthoracic Doppler echocardiography and cold pressor test. Proposed reasons for this could include a limited number of patients and lower ranolazine dose. This study did find an improvement in brachial artery flow– mediated dilation with ranolazine. Results of our larger multicenter trial further address the knowledge gap and provide evidence supporting late sodium current inhibition as a novel mechanism to improve angina among patients with more-severe CMD.

Ranolazine is primarily thought to act via inhibition of the late sodium current channel in ischemic cardiac myocytes [25,26]. In cardiac myocytes, ischemia leads to pathological changes of voltage-gated sodium channels that cause an increased late sodium current. Increased intracellular sodium triggers an increase in influx of calcium into cardiomyocytes via the Na^{+}-Ca^{+} exchanger, which contributes to diastolic dysfunction via increased cardiac myofilament activation [26]. Increased cardiac myofilament activation and increased LV diastolic tension have the potential to further increase coronary microcirculatory resistance, thus limiting the ability to augment myocardial perfusion [15]. Repeated episodes of ischemia leads to impairment of cardiomyocyte function via inflammatory mechanisms and portends development of cardiac fibrosis, steatosis, and heart failure [27]. By blocking the late sodium channel current, ranolazine leads to decreased intracellular calcium, which reduces diastolic dysfunction, leading to improved myocardial blood flow and decreased angina. Other proposed mechanisms of action of ranolazine include nitric oxide–mediated vasodilation effect [28], anti-inflammatory effects [29], and myocardial metabolic shifts [30]. Identification of treatment targets for CMD is important, as patients with persistent angina and signs of ischemia remain at elevated risk for adverse outcomes despite no obstructive CAD [19]. Many of these patients are likely to have CMD that contributes to ischemia. It is worthwhile to note, however, that similar clinical presentations (i.e. angina in the absence of atherosclerotic obstructions) may be associated with different pathophysiologic mechanisms (presence or absence of CMD), thus it is important to identify the underlying pathophysiologic mechanism in order to design effective therapeutic strategies.

In these patients with CFR <2.5, ranolazine improved MPRI and angina scores, however similar results were not observed for subjects with CFR ≥2.5. Our prior studies in similar patient cohorts also found beneficial results were observed among those with CFR <2.5 [31,32]. Similarly, analysis of the relationship between major adverse outcomes and CFR in another cohort identified that a CFR <2.32 was associated with an increased risk for adverse outcomes [19]. In another study of 35 symptomatic subjects with non-obstructive CAD, lower baseline CFR was associated with improvement in CFR with ranolazine compared with placebo [33]. These findings suggest that those with more sever coronary microvascular dysfunction appear to respond favorably. Reasons for improved outcomes in patients with lower CFR need to be further elucidated.

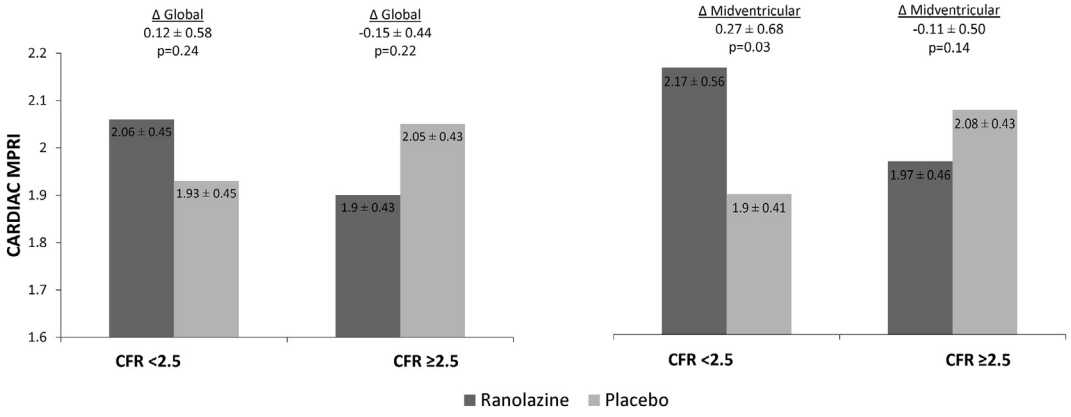

Fig. 2. Change in global and midventricular myocardial perfusion reserve index (MPRI) and in subgroups receiving ranolazine and placebo. CFR, coronary flow reserve.

Table 2
Comparison of relevant ranolazine studies in angina patients with no obstructive CAD.

	Mehta et al. [9]	Villano et al. [16]	Tagliamonte et al. [15]	Current study
Study design	Randomized, double blind, placebo controlled, crossover	Randomized, placebo controlled	Randomized, double blind, placebo controlled	Randomized, double blind, placebo controlled, crossover
Subjects	20 women with ≥10% ischemic myocardium by adenosine CMRI	37-women/9-men with positive ETT and CFR_{Ado} <2.5 (Doppler TTE)	19-women/39-men, with signs and symptoms of ischemia	81-women with CFR_{Ado} (Doppler invasive)
Treatments/duration	Ranolazine vs placebo 4 weeks	Ranolazine Ivabradine, or placebo 4 weeks	Ranolazine or placebo 8 weeks	Ranolazine vs placebo 2 weeks
Age, mean years ± SD	57 ± 11	57 ± 11	66 ± 10	55 ± 10
Assessments	SAQ and CMRI derived MPRI	SAQ, EuroQoL, EST, CFR_{Ado}, CFR_{CPT} and Brachial FMD	SAQ and Doppler TTE-derived CFR_{Dyprid}	SAQ, SAQ-7 and CMRI derived $MPRI_{Ado}$
Results	Ranolazine improved SAQ scores	Ranolazine improved SAQ and EuroQoL scales and EST duration. No effect on CFR or Brachial FMD	Ranolazine improved 4 of 5 SAQ domains and CFR	Ranolazine improved SAQ score and MPRI in patients with more severe CMD (CFR <2.5)
Conclusions	Ranolazine improved angina. Myocardial ischemia may also improve in women with low MPRI.	Ranolazine may have therapeutic role in patients with microvascular angina and inadequate symptom control.	Ranolazine improves CFR.	Ranolazine improved angina and myocardial perfusion in patients with severe CMD.

CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; EST, exercise stress test; ETT, exercise tolerance test; EuroQoL: European Quality of Life; FMD, flow-mediated dilation; MPRI, myocardial perfusion reserve index; SAQ, Seattle Angina Questionnaire; SD: standard deviation; TTE, transthoracic echocardiography.

In addition, although midventricular and global MPRI were improved in subjects with CFR <2.5 taking ranolazine, the magnitude of improvement was statistically significant at the midventricular region, suggesting that ischemia by CMD may not necessarily be a diffuse process but instead a patchy process more localized to the mid wall region. In a another study comparing gadolinium-enhanced CMRI at rest and stress in subjects with suspected CMD and healthy subjects, 56% of those with CMD (vs 0% of healthy subjects) had reversible perfusion defects [34]. Of note, those perfusion defects were not global, but were more localized, again highlighting that perfusion defects due to CMD may not necessarily be a diffuse process.

Future research should focus on the numerous knowledge gaps in the area of IHD with non-obstructive CAD and CMD [35]. As this disorder predominates among women, emphasis should be placed on this population to better explain mechanisms and also reduce morbidity and mortality [36]. MPRI may not be sufficiently accurate to best assess impaired CFR compared with invasive assessment. Thus, further research is required to better standardize CMRI approaches to measuring CFR. Currently, standard tests for CMD include invasive CRT [35] and non-invasive positron emission tomographic myocardial perfusion imaging as the reference standard noninvasive method of measuring absolute CFR [37].

Based on the work summarized above, there is a reasonable feasibility signal that late sodium channel inhibition may be useful (Table 2), the degree of late sodium channel inhibition to best optimize myocardial perfusion is critical but unknown. Current dosing ranolazine regimens (long acting with twice daily dosing and limited to 1000 mg) were developed for patients with angina and obstructive CAD, and may not be optimal for non-obstructive CAD with CMD. Ranolazine at different doses, more potent derivatives, along with other drugs with late sodium channel inhibition activity, should be explored.

4.1. Study strengths and limitations

Our study is the largest trial and only multicenter trial comparing the effects of ranolazine in patients with findings consistent with CMD documented by invasive testing. Other strengths include a rigorous double-blind crossover design, use of validated measures and core labs masked to patient characteristics and treatment assignment, and CMRI and CRT evaluation. It is potentially limited by the short-term exposure to ranolazine; however, a similar duration was used in a dose-ranging ranolazine trial of angina patients with obstructive CAD [38]. An additional limitation may be using the SAQ to assess atypical symptoms, which is potentially problematic with only 2-week study administration. While we objectively assessed MPRI, a validated semi-quantitative myocardial perfusion reserve index, MPRI is based on the relative upslopes of arrival of myocardial gadolinium contrast during adenosine stress and at rest. While MPRI correlates with CFR, it is not a direct measure of myocardial blood flow or CFR. Higher doses of ranolazine (1000 mg twice daily) are not readily available in Europe and other countries. Further analysis stratified based on the degree of coronary artery disease could not be performed. Lastly, our study consisted mostly of women and so results may not be generalized to men.

5. Conclusion

Short-term late sodium channel inhibition with ranolazine appears effective for reducing angina and increasing CMRI estimates of myocardial perfusion in women with no obstructive CAD and CMD defined as CFR <2.5. A direct correlation between higher MPRI and improvement in symptoms was observed, indicating that angina was related to ischemia. In this challenging-to-manage cohort, late sodium channel inhibition provides a promising management option.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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