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

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ABSTRACT

Purpose: The goal of this study was to investigate the effects of the antianginal drugs ranolazine, nicorandil, and ivabradine on coronary microvascular function.

Methods: Electronic scientific databases were searched for randomized trials investigating the effects of antianginal drugs on coronary microvascular function. Primary outcomes were changes in the coronary flow reserve (CFR), index of microvascular resistance (IMR), and myocardial perfusion reserve index (MPRI). The secondary outcome was the Seattle Angina Questionnaire scores. The standardized mean difference or weighted mean difference (WMD) (95% CI) served as a summary statistic.

Findings: The antianginal drugs ranolazine, nicorandil, and ivabradine did not increase the CFR compared with the control drugs (standardized mean difference, 0.39; 95% CI, −0.08 to 0.85; $P = 0.10$). Ranolazine did not increase the global MPRI compared with the control drugs (weighted mean difference [WMD], 0.11; 95% CI, −0.06 to 0.29; $P = 0.21$). However, in the subgroups with a baseline CFR <2.5 or a global MPRI <2, ranolazine increased the global MPRI (WMD, 0.19; 95% CI, 0.10 to 0.27; $P < 0.0001$). In addition, the subendocardial midventricular MPRI (mid-subendocardial MPRI) was improved after ranolazine treatment (WMD, 0.12; 95% CI, 0.03 to 0.20; $P = 0.007$). Moreover, nicorandil significantly reduced the IMR compared with the control drugs (WMD, −7.63; 95% CI, −11.82 to −3.44; $P = 0.0004$). In addition, ranolazine and ivabradine improved 3 of the 5 Seattle Angina Questionnaire scores.

Implications: Ranolazine improved the global MPRI in patients with definite coronary microvascular dysfunction and the mid-subendocardial MPRI with suspicious coronary microvascular dysfunction, and nicorandil reduced the IMR. In addition, ranolazine and ivabradine reduced angina. Moreover, it is possible that the IMR and mid-subendocardial MPRI are more sensitive than the CFR and global MPRI for evaluating coronary microvascular function. (*Clin Ther*. 2019;41:2137–2152)

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Key words: coronary flow reserve, coronary microvascular dysfunction, coronary microvascular function, index of microvascular resistance, ivabradine, myocardial perfusion reserve index, nicorandil, ranolazine.

INTRODUCTION

After >20 years of investigation, the methods assessing coronary microcirculation function have been established, namely, invasive or noninvasive tests of coronary microvascular function.[1] However, the treatment of coronary microcirculation dysfunction (CMD) is still in the preliminary stages of investigation, and most of the conclusions about its treatment come from a few clinical cases and empirical inferences. Studies have shown that CMD can cause myocardial ischemia, and the persistence of CMD is associated with the occurrence of major adverse cardiovascular events (MACE).[2,3] In addition, according to incomplete statistics from relevant studies such as WISE (Women's Ischaemia Syndrome Evaluation) in the United States, the costs associated with persistent chest pain, repeat utilization of health services, and poor patient function caused by suspicious CMD have reached as high as $13 billion, which is only the conclusion drawn in the case of incomplete and data lag.[4–6] These physical hazards and economic burdens highlight the need for CMD treatment.

Empirical treatment of CMD is based on traditional therapies for coronary heart disease, including antiplatelet, lipid-lowering, and anti-ischemic therapy (eg, beta-blockers, nitrates, angiotensin-converting enzyme inhibitors). However, the curative effect of experiential therapy alone on CMD is not evident.[7,8] Multiple novel drugs that primarily reduce angina, including ranolazine, ivabradine, and nicorandil, have been evaluated in patients with CMD.[9–11] Ranolazine reportedly improves myocardial perfusion by reducing sodium and calcium overload, thereby improving the relaxation and diastolic stiffness of cardiomyocytes.[12] Ivabradine is a specific bradycardia agent that directly inhibits sinoatrial node activity.[13] Nicorandil is thought to mimic ischemic preconditioning to protect cardiomyocytes,[14] and these 3 drugs are believed to alleviate angina symptoms by improving myocardial perfusion. However, recent randomized controlled trials (RCTs) have shown that ranolazine and ivabradine do not improve angina symptoms or microvascular function in patients with CMD.[15,16]

The inconsistency of data from randomized trials in this field regarding the efficacy of these drugs may be due to the small-sample trials. We therefore performed a meta-analysis including eligible RCTs for the first time to assess the protective effects of the non–first-line antianginal drugs on the improvement of angina symptoms and microvascular function.

MATERIALS AND METHODS

Data Sources

The MEDLINE, EMBASE, and Cochrane databases and the reference lists found in original and review articles were searched independently by 2 reviewers using Medical Subject Headings terms, key words, titles, and abstracts. The search terms were "coronary flow reserve (CFR)," "index of microvascular resistance (IMR)," and "myocardial perfusion reserve index (MPRI)," paired with "ranolazine," "nicorandil," and "ivabradine." All historical literature was searched until July 2019. Language was limited to English only.

Study Selection

An initial eligibility screen of all retrieved titles and abstracts was conducted, and original studies were included in the present meta-analysis if they met the following criteria: (1) participants were human subjects and had typical symptoms of myocardial ischemia; (2) at least 1 coronary microvascular function test, including CFR, IMR, and MPRI, was performed in the included subjects; (3) the participants were randomly assigned to receive ranolazine or ivabradine or nicorandil in the treatment group and placebo in the control group; and (4) inclusion required sufficient data, including CFR, IMR, and MPRI results and Seattle Angina Questionnaire (SAQ) scores.

Based on the evaluation of the abstract, the full text was obtained. Only fully published trials were included. The primary outcomes were the changes in CFR, IMR, and MPRI. The secondary outcome was the SAQ scores, which included 5 indicators: physical limitation, angina stability, angina frequency, treatment satisfaction, and quality of life (QoL). Two investigators independently reviewed all full-text

articles that potentially met the inclusion criteria according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[17] In cases of disagreement, a consensus was obtained by discussion with a third author.

The exclusion criteria were as follows: (1) non-RCTs; (2) articles with incomplete or erroneous data; and (3) patients with obstructive coronary artery disease (OCAD) without percutaneous coronary intervention (PCI) treatment. Because the detection of coronary microvascular function is affected by the degree of epicardial coronary stenosis, patients with OCAD were excluded. The definition of OCAD was based on findings from the Clinical Assessment, Reporting, and Tracking Program in which the left main stenosis was >50% and the other coronary stenosis was >70%.[18]

Data Extraction and Quality Assessment

The methods of data extraction are outlined in our previous study.[19] All selected articles were reviewed by 2 reviewers, who independently extracted data to a data sheet. Data extraction included the year of publication, study design, sample size, patient characteristics, inclusion and exclusion criteria, control and intervention protocols, randomization, and blinding, as well as the outcome parameters described earlier. After the extraction of relevant data by the 2 authors, data were examined for possible inconsistencies that were then resolved by discussion, and if consensus could not be reached, a third author was consulted. Studies were not conducted directly on humans, and ethical approval was therefore not necessary.

Two authors used the 7 domains of the Cochrane risk of bias tool to evaluate the quality of the included studies, using the following criteria: randomization sequence generation, concealment of randomization sequence, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Studies were classified as having low risk, high risk, or unclear risk of bias for each item, as suggested in the Cochrane handbook.[20]

Statistical Analysis

The verified data were analyzed by using Stata software version 13.0 (StataCorp, College Station, Texas) and RevMan software version 5.2 (Cochrane Collaboration, Oxford, United Kingdom). One investigator entered the data, and another investigator verified the data entry. The standardized mean difference (SMD) or weighted mean difference (WMD) (95% CI) served as a summary statistic. According to section 9.4.5.1 of the Cochrane handbook,[21] the WMD was selected when the results of the trial were tested by the same tool; otherwise, the SMD was selected. Therefore, the results of CFR in this study were combined with SMD because its measurement came from a variety of methods (positron emission tomography-computed tomography [PET-CT] imaging, echocardiography, and thermodilution techniques). The heterogeneity test was assessed with a χ^2-based Q test. When this $P_{\text{heterogeneity}}$ is < 0.1, the summary results are considered to be heterogeneous; otherwise, there is no heterogeneity. If there is heterogeneity in the summary results, assessing the degree of heterogeneity is conducted with an I^2 test ($I^2 = 0\%-25\%$, no heterogeneity; $I^2 = 25\%-50\%$, moderate heterogeneity; $I^2 = 50\%-75\%$, large heterogeneity; and $I^2 = 75\%-100\%$, extreme heterogeneity). A fixed effects model was used if $P_{\text{heterogeneity}}$ was >0.1. However, if $P_{\text{heterogeneity}}$ was <0.1, a sensitivity analysis was used to assess the stability of the results. If the results of the sensitivity analysis were stable, the heterogeneity analysis was then conducted to explore the sources of heterogeneity, and the results were modeled by using a random effects model. If the results of the sensitivity analysis were unstable, outlier trials were analyzed, and if the trials had sufficient reasons to be excluded, then after the exclusions, the remaining trials were aggregated and tested for heterogeneity.

Meta-regression analyses were used to assess the impact of several covariates on primary or secondary outcomes with statistical significance and heterogeneity. R^2 represented the covariate to explain the degree of heterogeneity, and a P value < 0.05 represented the covariate as a source of heterogeneity. The following covariates were included: age, proportion of women, hypertension, diabetes, hyperlipidemia, smoking rate, body mass index (BMI), family history of coronary artery disease (CAD), diagnosis of CMD (suspicious/definite), and type of clinical trial (parallel/cross). In addition, due to the small amount of data associated with this meta-analysis, 3 non–first-line antianginal

drugs with different mechanisms to improve myocardial perfusion were included. Thus, according to section 5.6 of the Cochrane handbook,[22] the broad scope of systematic review was adopted, and subgroup analysis was conducted to establish the effect of between-study clinical heterogeneity on the conclusions of the meta-analysis.

In addition, because the efficacy of antianginal drugs in patients with definite CMD is an important and interesting end point, these related data were also extracted for subgroup statistics. According to the related studies of CMD,[1,23] definite CMD should be diagnosed in accordance with the following 3 points: (1) typical symptoms of myocardial ischemia; (2) an absence or resolution of OCAD; and (3) presence of abnormalities on coronary microvascular function tests (baseline CFR <2.5 or global MPRI <2 or IMR >25). Suspicious CMD is defined as satisfying the first 2 points. An intervention was assumed to have had a significant effect if the 95% CI did not include the value 0 for the SMD or WMD. Publication bias was assessed by using funnel plot techniques and Egger's test.

RESULTS

Literature Search

The literature search identified 32 records of clinical trials in MEDLINE, 74 records in EMBASE, and 47 records in the Cochrane databases (Figure 1). After checking for duplicates, 34 unique and fully published articles remained. A brief review of the abstract and manuscript of these 34 articles resulted in 9 studies that were appropriate for detailed review; all 9 were included in the meta-analysis.[9–11,15,16,24–27] The remaining 25 articles were excluded because they met the exclusion criteria.[28–52] Specifically, 6 studies were excluded because they were non-RCTs, and 8 studies were excluded because they were reviews. Two studies were excluded because there was no end point of interest. Three studies were excluded because they were case reports. One study was excluded because the patients they included had OCAD, and 1 study was excluded because it was not possible to determine if the patients included had non-OCAD. One study was excluded because the full text was Japanese, and one was excluded because the data were incomplete. The studies of Rambarat et al[51] and Birkeland et al[52] were subtrials of the study by Bairey et al.[15]

Characteristics of Included Studies

The main characteristics of these studies are reported in Supplemental Table I (in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Briefly, patients with myocardial ischemia and suspected CMD were randomly assigned to the antianginal drug (ranolazine, nicorandil, or ivabradine) group versus the control group. A parallel design was adopted in 4 trials. In the remaining trials, a cross design was adopted, but one of the trials[26] did not have a washout period, resulting in an imbalance of baseline data between the intervention group and the control group in protocol 2; consequently, protocol 2 was excluded. In 7 trials, ranolazine was used as an interventional drug for the treatment of CMD,[9,10,15,16,24,25,27] and one trial included ivabradine in addition to ranolazine.[16] In the remaining 2 trials, nicorandil was tested to treat CMD. In 7 trials, the control group was the placebo group.[9–11,15,16,25,27] In the remaining 2 trials, the control group was isosorbide 5-mononitrate or nitroglycerin. Those patients who experienced adverse events reduced the dosage of the intervention drug or were excluded from subsequent randomized allocation. All subjects who were enrolled received the assigned treatments in addition to other cardioactive therapies.

Coronary microvascular function is measured by using invasive or noninvasive methods. Invasive methods include intracoronary Doppler guidewire or thermodilution techniques.[11,26] Noninvasive technologies include PET-CT imaging, cardiac magnetic resonance imaging, and Doppler ultrasound systems.[9,10,15,16,24,25,27] In 8 trials, CFR was used as one of the indicators for assessing changes in coronary microvascular function.[9–11,15,16,24,25,27] At the same time, the MPRI and IMR were used as indicators of coronary microvascular function in some trials.[10,11,15,16]

The clinical features of the included patients were well balanced among the treatment arms in all the studies. A total of 650 subjects from 9 pilot trials were included in this meta-analysis. The main clinical features of the patients are shown in Supplemental Table II (in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Briefly, the median

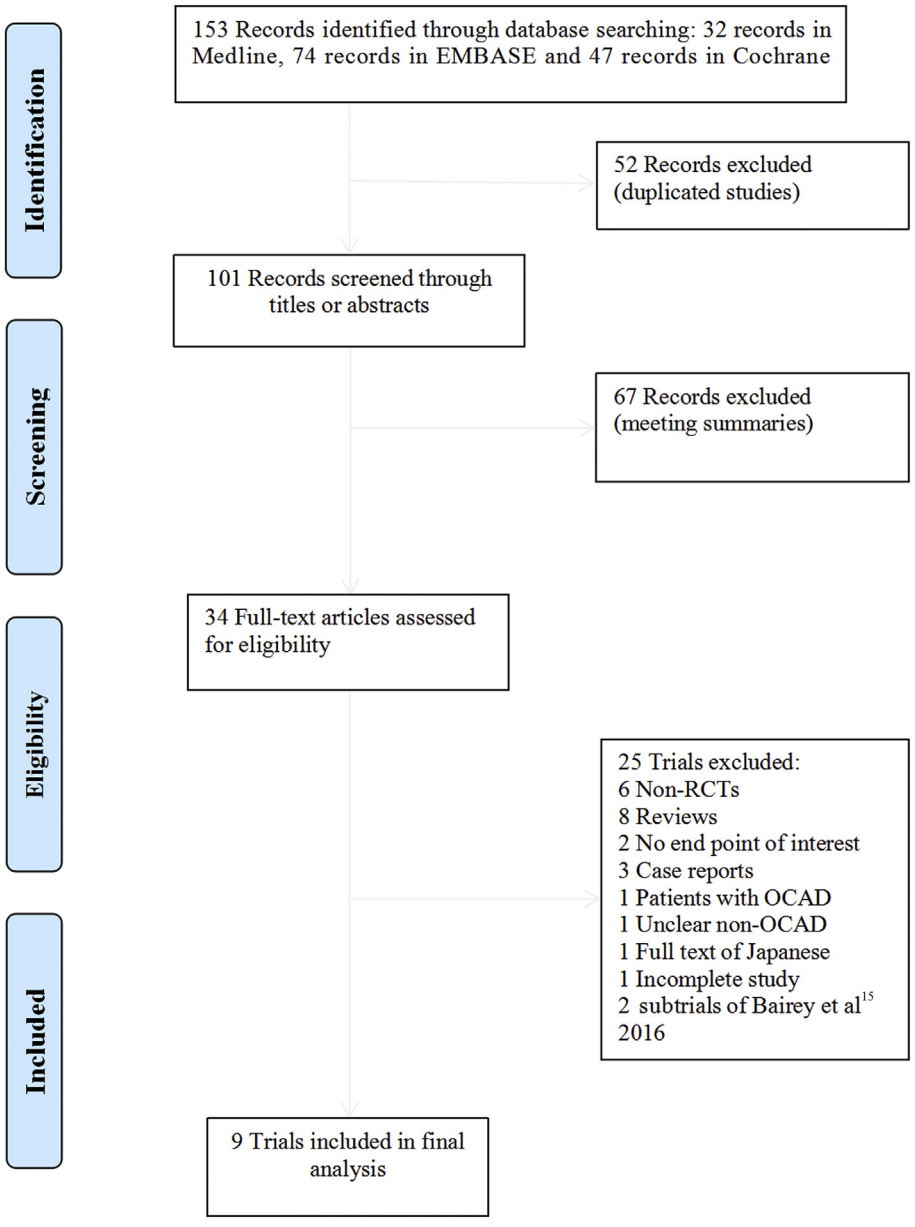


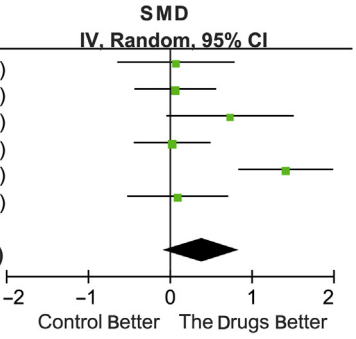
Figure 1. Flow diagram of study search and selection. OCAD = obstructive coronary artery disease; RCT = randomized controlled trial. Figure is from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(6): e1000097.

(range) age was 64.0 years (56.1−66.4 years), 49% (19.6%−88.2%) were women, and 63.3% (53.6%−78.1%), 29% (22.4%−47.0%), 55% (50.2%−78.5%), 41.7% (17.6%−60.0%), and 3.9% (0.4%−11.3%) corresponded to patients with hypertension, diabetes, hyperlipidemia, smoking, and current smoking, respectively. In addition, the average BMI was 28.0 kg/m^2 (range, 26.3−31.4 kg/m^2), and 53% (range, 31%−70%) of patients had a family history of CAD. In both studies,[11,26] intervention drugs were administered after PCI, and the remaining 7 trials included patients with non-OCAD.

A CFR

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	SMD IV, Random, 95% CI
Golino 2018	1.18	0.15	15	1.17	0.13	15	15.0%	0.07 (-0.65 to 0.79)
Hirohata 2014	3.2	1.7	33	3.1	1.5	29	18.4%	0.06 (-0.44 to 0.56)
Safdar 2017	1.9	0.4	21	1.6	0.4	10	14.1%	0.73 (-0.05 to 1.51)
Shah 2017	1.82	0.83	35	1.8	0.9	35	18.9%	0.02 (-0.45 to 0.49)
Tagliamonte 2015	2.54	0.44	29	1.99	0.32	29	17.1%	1.41 (0.83 to 1.99)
Villano 2013	1.78	0.4	31	1.74	0.5	15	16.5%	0.09 (-0.53 to 0.71)
Total (95% CI)			**164**			**133**	**100.0%**	**0.39 (-0.08 to 0.85)**

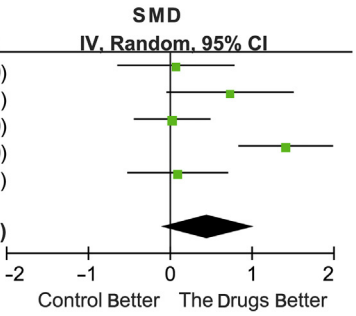
Heterogeneity: Tau² = .24; χ^2 = 18.22, *df* = 5 (*P* = .003); I^2 = 73%
Test for overall effect: *Z* = 1.63 (*P* = .10)



B Baseline CFR < 2.5

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	SMD IV, Random, 95% CI
Golino 2018	1.18	0.15	15	1.17	0.13	15	18.7%	0.07 (-0.65 to 0.79)
Safdar 2017	1.9	0.4	21	1.6	0.4	10	17.7%	0.73 (-0.05 to 1.51)
Shah 2017	1.82	0.83	35	1.8	0.9	35	22.6%	0.02 (-0.45 to 0.49)
Tagliamonte 2015	2.54	0.44	29	1.99	0.32	29	20.8%	1.41 (0.83 to 1.99)
Villano 2013	1.78	0.4	31	1.74	0.5	15	20.2%	0.09 (-0.53 to 0.71)
Total (95% CI)			**131**			**104**	**100.0%**	**0.46 (-0.10 to 1.02)**

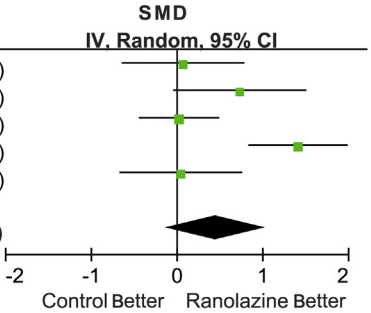
Heterogeneity: Tau² = .31; χ^2 = 16.62, *df* = 4 (*P* = .002); I^2 = 76%
Test for overall effect: *Z* = 1.60 (*P* = .11)



C Ranolazine and baseline CFR <2.5

Study or Subgroup	Ranolazine Mean	SD	Total	Control Mean	SD	Total	Weight	SMD IV, Random, 95% CI
Golino 2018	1.18	0.15	15	1.17	0.13	15	19.0%	0.07 (-0.65 to 0.79)
Safdar 2017	1.9	0.4	21	1.6	0.4	10	18.1%	0.73 (-0.05 to 1.51)
Shah 2017	1.82	0.83	35	1.8	0.9	35	22.8%	0.02 (-0.45 to 0.49)
Tagliamonte 2015	2.54	0.44	29	1.99	0.32	29	21.1%	1.41 (0.83 to 1.99)
Villano 2013	1.76	0.4	15	1.74	0.5	15	19.0%	0.04 (-0.67 to 0.76)
Total (95% CI)			**115**			**104**	**100.0%**	**0.46 (-0.12 to 1.04)**

Heterogeneity: Tau² = .33; χ^2 = 16.57, *df* = 4 (*P* = .002); I^2 = 76%
Test for overall effect: *Z* = 1.54 (*P* = .12)



D Ranolazine and corrected CFR

Study or Subgroup	Ranolazine Mean	SD	Total	Control Mean	SD	Total	Weight	SMD IV, Random, 95% CI
Golino 2018	1	0.13	15	1	0.11	15	23.0%	0.00 (-0.72 to 0.72)
Safdar 2017	1.9	0.4	21	1.6	0.4	35	25.4%	0.74 (0.18 to 1.30)
Shah 2017	1.64	0.87	35	1.64	0.87	35	26.7%	0.00 (-0.47 to 0.47)
Tagliamonte 2015	2.36	0.41	29	1.83	0.29	29	25.0%	1.47 (0.89 to 2.06)
Total (95% CI)			**100**			**114**	**100.0%**	**0.56 (-0.14 to 1.25)**

Heterogeneity: Tau² = .41; χ^2 = 17.54, *df* = 3 (*P* = .0005); I^2 = 83%
Test for overall effect: *Z* = 1.57 (*P* = .12)

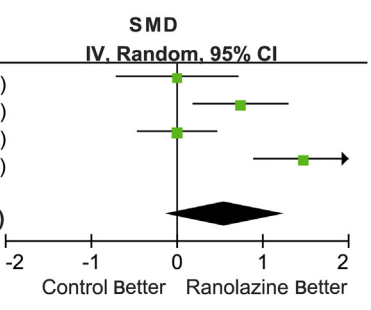


Figure 2. Forest plot of primary outcomes of coronary flow reserve (CFR). (A) Forest plot showing the effects of the antianginal drugs (ranolazine, ivabradine, and nicorandil) on the change in CFR. (B) Forest plot showing the effects of the antianginal drugs (ranolazine and ivabradine) on the change in CFR in the subgroup with baseline CFR <2.5. (C) Forest plot showing the effects of ranolazine on the change in

Primary Outcomes

The antianginal drugs (ranolazine, ivabradine, and nicorandil) did not increase the CFR compared with the control drugs (SMD, 0.39; 95% CI, −0.08 to 0.85; $P = 0.10$; $\chi^2 = 18.22$; $I^2 = 73\%$; $P_{heterogeneity} = 0.003$) (Figure 2A). Sensitivity analysis revealed that the study by Tagliamonte et al[27] may be the source of statistical heterogeneity in the meta-analysis for the CFR end point (see Supplemental Figure 1A in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). When this outlier study was removed, there was no evidence of heterogeneity in the 5 remaining studies ($\chi^2 = 2.61$; $I^2 = 0\%$; $P_{heterogeneity} = 0.63$), but these 5 trials still showed no significant change in the CFR with the antianginal drugs (SMD, 0.13; 95% CI, −0.13 to 0.39; $P = 0.33$) (see Supplemental Figure 1B in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

In the baseline CFR <2.5 subgroup,[9,16,23,24,26] CFR did not improve after treatment with the antianginal drugs (ranolazine and ivabradine) (SMD, 0.46; 95% CI, −0.10 to 1.02; $P = 0.11$; $\chi^2 = 16.62$; $I^2 = 76\%$; $P_{heterogeneity} = 0.002$) (Figure 2B). After the study by Tagliamonte et al was excluded by sensitivity analysis (see Supplemental Figure 1C in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008), no heterogeneity was found in the remaining 4 trials ($\chi^2 = 2.51$; $I^2 = 0\%$; $P_{heterogeneity} = 0.47$), but these 4 trials still showed no significant change in the CFR after treatment with the antianginal drugs (SMD, 0.16; 95% CI, −0.15 to 0.46; $P = 0.31$) (see Supplemental Figure 1D in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

In the trials of ranolazine for definite CMD (baseline CFR <2.5), the CFR did not increase significantly (SMD, 0.46; 95% CI, −0.12 to 1.04; $P = 0.12$; $\chi^2 = 16.57$; $I^2 = 76\%$; $P_{heterogeneity} = 0.002$) (Figure 2C). After the study by Tagliamonte et al was excluded by sensitivity analysis (see Supplemental Figure 1E in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008), the remaining 4 trials still showed no significant change in the CFR with ranolazine treatment (SMD, 0.15; 95% CI, −0.16 to 0.47; $P = 0.35$; $\chi^2 = 2.56$; $I^2 = 0\%$; $P_{heterogeneity} = 0.47$) (see Supplemental Figure 1F in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). In addition, after CFR was corrected for heart rate and systolic blood pressure, ranolazine did not increase the corrected CFR compared with the control drugs (SMD, 0.56; 95% CI, −0.14 to 1.25; $P = 0.12$; $\chi^2 = 17.54$; $I^2 = 83\%$; $P_{heterogeneity} = 0.0005$) (Figure 2D).

Ranolazine did not increase the global MPRI compared with the control drugs (WMD, 0.11; 95% CI, −0.06 to 0.29; $P = 0.21$; $\chi^2 = 6.01$; $I^2 = 83\%$; $P_{heterogeneity} = 0.01$) (Figure 3A). However, in the subgroup with a baseline CFR <2.5 or global MPRI <2, ranolazine increased the global MPRI (WMD, 0.19; 95% CI, 0.10 to 0.27; $P < 0.0001$; $\chi^2 = 0.35$; $I^2 = 0\%$; $P_{heterogeneity} = 0.55$) (Figure 3B). In addition, subendocardial midventricular MPRI (mid-subendocardial MPRI) improved after treatment with ranolazine (WMD, 0.12; 95% CI, 0.03 to 0.20; $P = 0.007$; $\chi^2 = 2.60$; $I^2 = 62\%$; $P_{heterogeneity} = 0.11$) (Figure 3C). Moreover, nicorandil significantly improved the IMR compared with the control drug (WMD, −7.63; 95% CI, −11.82 to −3.44; $P = 0.0004$; $\chi^2 = 0.01$; $I^2 = 0\%$; and $P_{heterogeneity} = 0.94$) (Figure 3D).

Secondary Outcomes

The antianginal drugs (ranolazine and ivabradine) increased the SAQ physical limitation score compared with the control drugs (WMD, 5.63; 95% CI, 3.53 to 7.73; $P < 0.001$; $\chi^2 = 4.77$; $I^2 = 37\%$; $P_{heterogeneity} = 0.19$) (Figure 4A). Subgroup analysis showed that ranolazine could also increase the SAQ physical limitation score compared with the control drugs (WMD, 6.10; 95% CI, 2.38 to 9.82; $P = 0.001$; $\chi^2 = 6.56$; $I^2 = 54\%$; $P_{heterogeneity} = 0.09$)

CFR in the subgroup with baseline CFR <2.5. (D) Forest plot showing effects of ranolazine on the change in the corrected CFR in the subgroup with baseline CFR <2.5. A significant effect of ranolazine was assumed if the 95% CI did not include the value 0 for the standardized mean difference (SMD). IV = inverse variance; SBP = systolic blood pressure. CFR calculation = peak global left ventricular myocardial blood flow (MBF)/rest MBF. Corrected CFR calculation = peak global left ventricular MBF/(rest MBF/(rest heart rate × rest SBP) × 10,000).

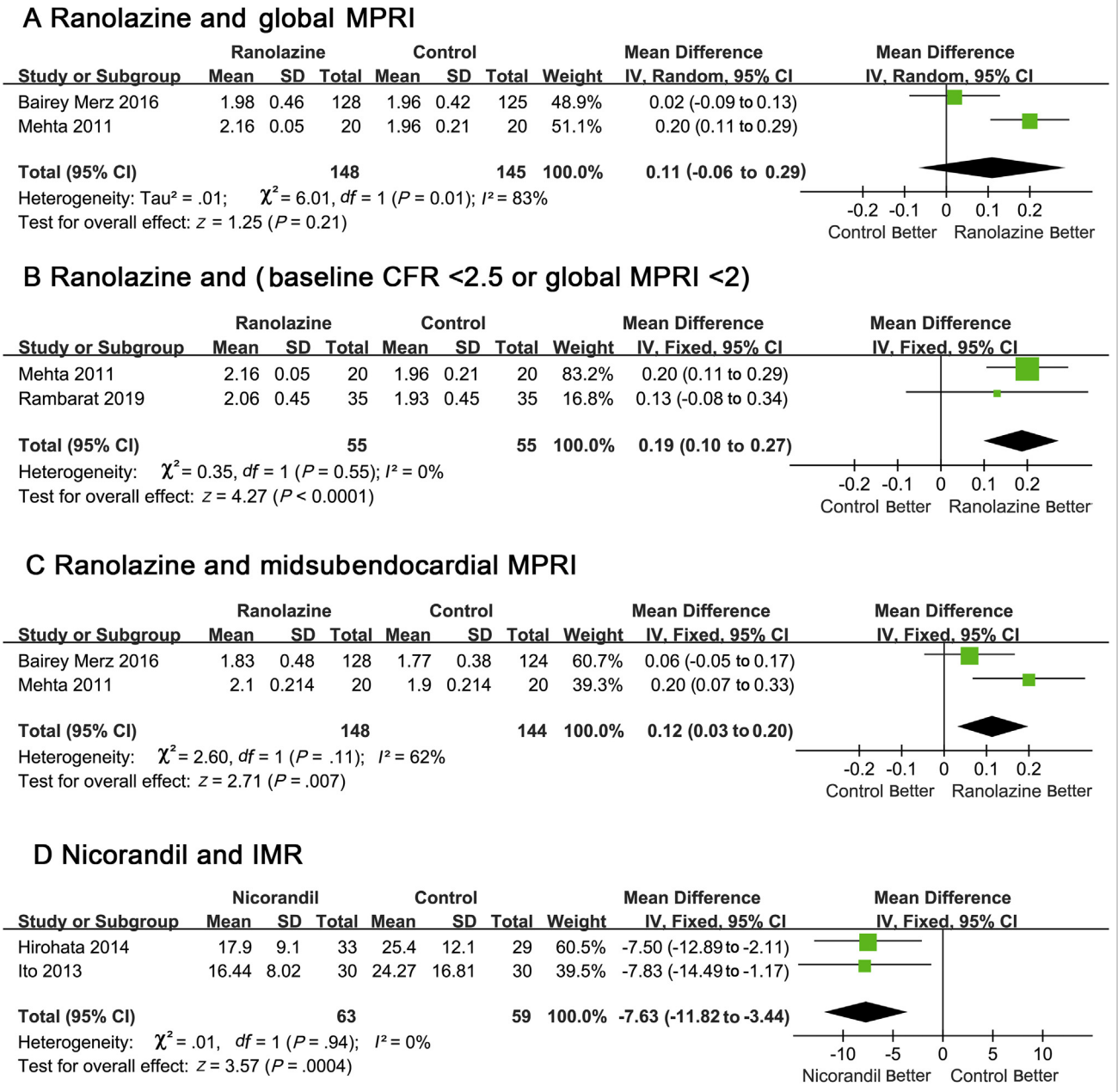


Figure 3. Forest plot of the primary outcomes of myocardial perfusion reserve index (MPRI) and index of microvascular resistance (IMR). (A) Forest plot showing the effects of ranolazine on the change in the global MPRI. (B) Forest plot showing the effects of ranolazine on the change in the global MPRI in the baseline coronary flow reserve (CFR) < 2.5 or MPRI <2.0 subgroup. (C) Forest plot showing the effects of ranolazine on the change in the subendocardial midventricular MPRI (mid-subendocardial MPRI). (D) Forest plot showing effects of nicorandil on the change in the IMR. A significant effect of ranolazine was assumed if the 95% CI did not include the value 0 for the weighted mean difference. IV = inverse variance.

(see Supplemental Figure 2A in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

The SAQ angina stability score was improved with the antianginal drugs (ranolazine and ivabradine) (WMD, 16.95; 95% CI, 8.45 to 25.45; $P < 0.001$; $\chi^2 = 12.21$; $I^2 = 75\%$; $P_{heterogeneity} = 0.007$) (Figure 4B). Sensitivity analysis did not reveal the source of heterogeneity (see Supplemental Figure 2B in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Meta-regression analysis showed that BMI or definite CMD may be the source of heterogeneity in angina stability, but there was no statistically significant difference ($R^2 = 100\%$, $P = 0.075$; $R^2 = 100\%$, $P = 0.082$, respectively) (see Supplemental Figure 2C in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Subgroup analysis showed that ranolazine could also increase the SAQ angina stability score compared with the control drugs (WMD, 17.23; 95% CI, 13.35 to 21.11; $P < 0.001$; $\chi^2 = 17.5$; $I^2 = 83\%$; $P_{heterogeneity} = 0.0006$) (see Supplemental Figure 2D in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

The antianginal drugs (ranolazine and ivabradine) did not increase the SAQ angina frequency score compared with the control drugs (WMD, 6.86; 95% CI, −0.60 to 14.32; $P = 0.07$; $\chi^2 = 13.17$; $I^2 = 77\%$; $P_{heterogeneity} = 0.004$) (Figure 4C). Sensitivity analysis did not reveal the source of heterogeneity (see Supplemental Figure 2E in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Subgroup analysis showed that ranolazine also failed to increase the SAQ angina frequency score compared with the control drugs (WMD, 7.63; 95% CI, −0.01 to 15.26; $P = 0.05$; $\chi^2 = 13.18$; $I^2 = 77\%$; $P_{heterogeneity} = 0.004$) (see Supplemental Figure 2F in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

There was no difference in treatment satisfaction between the antianginal drugs (ranolazine and ivabradine) group and the control drugs group (WMD, 0.18; 95% CI, −5.44 to 5.80; $P = 0.95$; $\chi^2 = 16.15$; $I^2 = 81\%$; $P_{heterogeneity} = 0.001$) (Figure 4D). Sensitivity analysis revealed that the study by Villano et al[16] may be the source of data heterogeneity (see Supplemental Figure 2G in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). When this outlier study was removed, there was no evidence of heterogeneity in the remaining 3 studies ($\chi^2 = 1.95$; $I^2 = 0\%$; $P_{heterogeneity} = 0.38$), and these 3 trials showed that treatment with the antianginal drugs reduced treatment satisfaction (WMD, −3.28; 95% CI, −5.62 to −0.94; $P = 0.006$) (see Supplemental Figure 2H in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Subgroup analysis showed that ranolazine also failed to increase the treatment satisfaction compared with the control drugs (WMD, −3.28; 95% CI,−5.62 to −0.94; $P = 0.006$; $\chi^2 = 1.95$; $I^2 = 0\%$; $P_{heterogeneity} = 0.38$) (see Supplemental Figure 2I in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). When this outlier study was removed, the results were consistent with those discussed earlier.

The QoL score improved with the antianginal drugs (ranolazine and ivabradine) (SMD, 1.00; 95% CI, 0.07 to 1.92; $P = 0.04$; $\chi^2 = 38.13$; $I^2 = 92\%$; $P_{heterogeneity} < 0.001$) (Figure 4E). Sensitivity analysis did not reveal the source of heterogeneity (see Supplemental Figure 2J in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Meta-regression analysis showed that the duration of the drug intervention was the source of the QoL heterogeneity ($R^2 = 94.27\%$; $P = 0.05$) (see Supplemental Figure 2K in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). Subgroup analysis showed that ranolazine could also increase the QoL score compared with the control drugs (SMD, 1.06; 95% CI, 0.07 to 2.04; $P < 0.05$; $\chi^2 = 38.98$; $I^2 = 92\%$; $P_{heterogeneity} < 0.001$) (see Supplemental Figure 2L in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

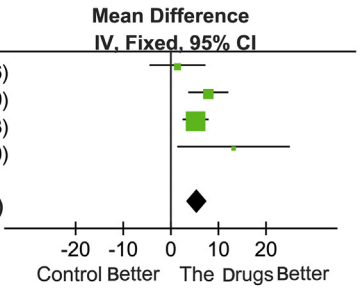
Quality of Studies, Clinical Heterogeneity, and Publication Bias

The quality assessment of the included studies is reported in Supplemental Figure 3 (in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008). All the studies mentioned randomized grouping except for Hirohata et al.[11] Three of the studies used computer-designated randomization and were considered to be low risk.[16,25,26] Other studies did not elaborate on the randomized methods used and were therefore considered unclear risk. Allocation concealment was not explicitly mentioned in all studies, and thus they were considered unclear risk. Six studies were blinded and considered to be low risk,[9,10,15,16,24,25,27] whereas the remaining 2 studies

A Physical limitation

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bairey Merz 2016	68.09	23.34	123	66.7	23.34	120	12.8%	1.39 (-4.48 to 7.26)
Mehta 2011	90.76	5	20	82.88	8.19	20	24.9%	7.88 (3.67 to 12.09)
Tagliamonte 2015	87.4	6.07	29	82.2	4.39	29	59.2%	5.20 (2.47 to 7.93)
Villano 2013	80.18	14.7	31	67	21	15	3.1%	13.18 (1.36 to 25.00)
Total (95% CI)			**203**			**184**	**100.0%**	**5.63 (3.53 to 7.73)**

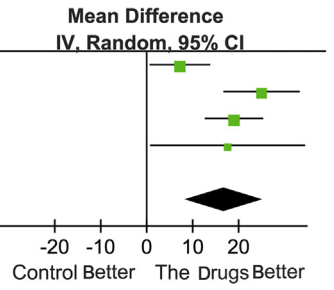
Heterogeneity: $\chi^2 = 4.77$, $df = 3$ ($P = .19$); $I^2 = 37\%$
Test for overall effect: $Z = 5.26$ ($P < .00001$)



B Angina stability

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bairey Merz 2016	58.4	26.11	128	51.17	27.68	128	29.2%	7.23 (0.64 to 13.82)
Mehta 2011	75	13.38	20	50	13.38	20	26.5%	25.00 (16.71 to 33.29)
Tagliamonte 2015	77.6	12.34	29	58.6	12.34	29	29.6%	19.00 (12.65 to 25.35)
Villano 2013	72.61	31.66	31	55	25	15	14.8%	17.61 (0.75 to 34.47)
Total (95% CI)			**208**			**192**	**100.0%**	**16.95 (8.45 to 25.45)**

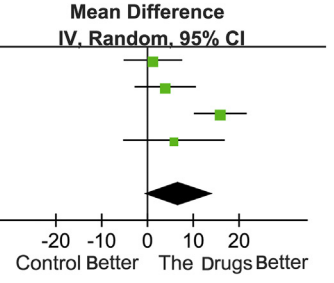
Heterogeneity: Tau² = 53.18; $\chi^2 = 12.21$, $df = 3$ ($P = .007$); $I^2 = 75\%$
Test for overall effect: $Z = 3.91$ ($P < .0001$)



C Angina frequency

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bairey Merz 2016	63.91	26.09	127	62.73	25.95	128	26.8%	1.18 (-5.21 to 7.57)
Mehta 2011	78.51	13.38	20	74.63	7.36	20	26.3%	3.88 (-2.81 to 10.57)
Tagliamonte 2015	80.7	12.34	29	64.8	9.8703	29	27.8%	15.90 (10.15 to 21.65)
Villano 2013	77.07	18	31	71.3	18	15	19.2%	5.77 (-5.33 to 16.87)
Total (95% CI)			**207**			**192**	**100.0%**	**6.86 (-0.60 to 14.32)**

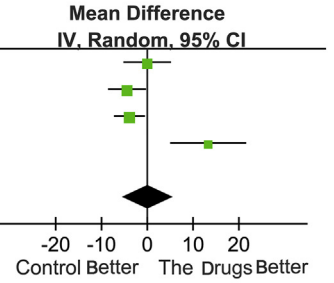
Heterogeneity: Tau² = 43.56; $\chi^2 = 13.17$, $df = 3$ ($P = .004$); $I^2 = 77\%$
Test for overall effect: $Z = 1.80$ ($P = .07$)



D Treatment satisfaction

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bairey Merz 2016	74.16	21.23	127	74.17	21.08	128	25.2%	-0.01 (-5.20 to 5.18)
Mehta 2011	87.5	6.69	20	91.93	6.69	20	27.3%	-4.43 (-8.58 to -0.28)
Tagliamonte 2015	86.4	7.26	29	90.3	5.8	29	28.7%	-3.90 (-7.28 to -0.52)
Villano 2013	87.5	12.27	31	74.2	14	15	18.9%	13.30 (5.00 to 21.60)
Total (95% CI)			**207**			**192**	**100.0%**	**0.18 (-5.44 to 5.80)**

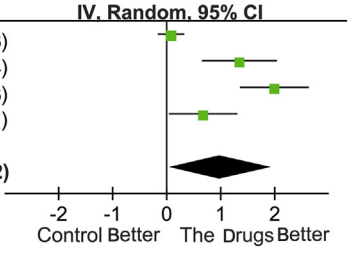
Heterogeneity: Tau² = 25.70; $\chi^2 = 16.15$, $df = 3$ ($P = .001$); $I^2 = 81\%$
Test for overall effect: $Z = .06$ ($P = .95$)



E QoL

Study or Subgroup	Antianginal drugs Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairey Merz 2016	56.05	23.09	128	54.17	23.31	128	27.1%	0.08 (-0.16 to 0.33)
Mehta 2011	74.06	6.13	20	66.69	4.47	20	23.9%	1.35 (0.65 to 2.04)
Tagliamonte 2015	77.6	8.24	29	62.9	6.17	29	24.5%	1.99 (1.36 to 2.63)
Villano 2013	75.79	15.57	31	64.3	19	15	24.5%	0.67 (0.04 to 1.31)
Total (95% CI)			**208**			**192**	**100.0%**	**1.00 (0.07 to 1.92)**

Heterogeneity: Tau² = 0.81; $\chi^2 = 38.13$, $df = 3$ ($P < .00001$); $I^2 = 92\%$
Test for overall effect: $Z = 2.11$ ($P = .04$)



used nonblinding and unclear blinding methods. Outcome observers in 5 studies[9,10,16,25,26] knew nothing about the treatment and distribution schemes, and the outcome analysis of the remaining study was performed by a third party,[15] and thus their detection bias was considered low risk. In 3 studies,[9,15,25] although participants dropped out halfway through the study, the final proportion of those who completed the study in both groups was almost the same as that in the beginning, and thus attrition bias was considered low risk. No selective bias or other bias was found in any of the studies.

In this meta-analysis, the data of CFR and SAQ scores were evaluated by the broad scope of systematic review. These results were consistent with those of subgroup analysis, which indicated that the clinical heterogeneity was acceptable.

The funnel plot in the trials of CFR was visually symmetric, and a statistical analysis of the funnel plot also suggested that no publication bias was present (Egger's test, $P = 0.724$) (see Supplemental Figure 4 in the online version at https://doi.org/10.1016/j.clinthera.2019.08.008).

DISCUSSION

This meta-analysis of randomized trials investigated the protective effects of the antianginal drugs ranolazine, nicorandil, and ivabradine on the coronary microcirculation. The main findings are as follows: (1) ranolazine improved the global MPRI in patients with definite CMD and the mid-subendocardial MPRI with suspicious CMD; (2) nicorandil improved coronary microvascular function, which was evaluated by using the IMR; and (3) ranolazine and ivabradine improved 3 of the 5 SAQ scores.

In the absence of obstructive stenosis, the coronary microcirculation is the main vascular system that regulates the oxygen supply to the whole heart because 80% of the perfusion pressure of the myocardium depends on the prearterioles (vessels <500 μm in diameter) and arterioles (vessels <200 μm in diameter) of the coronary microcirculatory system. In contrast, the 3 main branches of the coronary artery, which are often of clinical concern, provide only 10% of the resistance.[53] These observations underscore the rationale for treating disturbances in the coronary microcirculation. Previously, the coronary microvascular system could not be identified by using coronary angiography or CT imaging. Consequently, the etiology of cardiac syndrome X, cardiac syndrome Y, and no reflow phenomenon after PCI could not be determined at that time, although the cause was actually CMD.[7,53] However, with the advancement of medical technology, the diagnosis of CMD no longer relies solely on indirect diagnostic methods. Noninvasive techniques (PET, cardiac magnetic resonance imaging, and Doppler ultrasound) and invasive techniques (Doppler wire and thermodilution techniques) are now used to evaluate the resistance in the coronary microvascular system by measuring the velocity of coronary blood flow and other related data. The results from these studies are used in combination with clinical manifestations and coronary angiography to comprehensively diagnose CMD.[1,23] The level of treatment of CMD is limited by the degree to which it can be diagnosed. In the past, traditional empirical treatment has not brought much benefit to patients with CMD. For this reason, recently reported data after the upgrade of diagnostic technology have suggested that some non–first-line antianginal drugs may have additional benefits for patients with CMD.[9,11,51] However, because these studies are almost exclusively pilot trials, the lack of an adequate sample size strongly limits the interpretation of the results.

The present report represents a comprehensive meta-analysis of study-level data, including 9 randomized trials with 650 subjects. The component trials were specifically designed to assess the

Figure 4. Forest plot of secondary outcomes of the Seattle Angina Questionnaire. (A) Forest plot showing the effects of the antianginal drugs (ranolazine and ivabradine) on physical limitations. (B) Forest plot showing the effects of the antianginal drugs (ranolazine and ivabradine) on angina stability. (C) Forest plot showing the effects of the antianginal drugs (ranolazine and ivabradine) on angina frequency. (D) Forest plot showing the effects of the antianginal drugs (ranolazine and ivabradine) on treatment satisfaction. (E) Forest plot showing the effects of the antianginal drugs on quality of life (QoL). A significant effect of ranolazine was assumed if the 95% CI did not include the value 0 for the standardized mean difference/weighted mean difference. IV = inverse variance; QoL = quality of life.

protective effects of the antianginal drugs (ranolazine, nicorandil, and ivabradine) on the coronary microcirculation. By evaluating the effects on microvascular function and angina symptoms in the treatment group, this meta-analysis may potentially add relevant information on this topic.

A major finding is that the global MPRI is increased in patients with definite CMD after ranolazine treatment. However, if the baseline global MPRI is not <2, the results suggest that ranolazine does not significantly increase the global MPRI. However, ranolazine treatment still increases the mid-subendocardial MPRI in the absence of a baseline global MPRI <2. Moreover, in patients with a defined baseline CFR <2.5, ranolazine tends to improve the CFR, although the difference is not significant, and there is large statistical heterogeneity in the results. Bairey et al[15] suggested that the therapeutic effect of ranolazine could be explained by the fact that patients with a CFR <2.5 (ie, the presence of definite CMD) benefited more than patients with a CFR >2.5. However, this observation does not explain the finding of this meta-analysis that ranolazine did not significantly improve CFR even in patients with a baseline CFR <2.5.

In reviewing the trials in which nicorandil improved coronary microvascular function, our meta-analysis suggests that nicorandil improved the IMR even without a defined baseline IMR >25. In addition, the results of CFR with the antianginal drugs were consistent with those of ranolazine.

CFR is defined as the ratio of blood flow at maximum filling of the whole coronary artery to that at baseline, and the global MPRI reflects the perfusion of the whole heart.[54,55] In patients with non-OCAD, a small proportion of epicardial stenosis may still affect ~10% of perfusion pressure. In contrast, the mid-subendocardial MPRI and IMR, when responding to local (microcirculatory) perfusion or resistance, are less affected by the small percentage of epicardial stenosis than by the global MPRI and CFR.[56,57] Therefore, excluding the factors of sample size and different study designs, our team considered that the main findings may be interpreted as implying that ranolazine and nicorandil are important in protecting coronary microcirculation, and this is not limited to patients with CMD (CFR <2.5 or global MPRI <2 or IMR >25). In addition, the sensitivity of the global MPRI and CFR to coronary microvascular function is lower than that of the mid-subendocardial MPRI and IMR, and the difference in sensitivity depends mainly on the degree of epicardial stenosis.

The secondary end point shows that the antianginal drugs ranolazine and ivabradine improved the SAQ physical limitation score. In addition, the antianginal drugs ranolazine and ivabradine also increased the SAQ angina stability score, although this finding was accompanied by extreme statistical heterogeneity. Meta-regression analysis shows that the source of heterogeneity tends to be different in depending on BMI or CMD diagnosis. The higher the BMI, the greater is the likelihood of obesity, and some patients with CMD can present with symptoms consistent with syndrome X or microvascular angina. Therefore, from a clinical point of view, BMI differences and a definite diagnosis of CMD may be factors contributing to the heterogeneity of the SAQ physical limitation score.

In addition, ranolazine and ivabradine seem to reduce the SAQ treatment satisfaction score, which may be due to side effects of the drugs. The main side effects are nausea and vertigo induced by ranolazine.[9,15,25] In the study by Villano et al,[16] the SAQ treatment satisfaction score increased after treatment with ranolazine and ivabradine, which may have been due to chance. The QoL score improved with ranolazine and ivabradine treatment, although this finding was accompanied by extreme statistical heterogeneity. Meta-regression analysis showed that heterogeneity originated from the duration of the drug intervention. Angina pectoris is a symptom that recurs over a long time period, and short-term observations may underestimate the efficacy of the drugs. Therefore, from a clinical point of view, the duration of the drug intervention may be a factor contributing to the heterogeneity of the QoL score. In the evaluation of SAQ and QoL scores, ranolazine accounted for ~96% of the subjects, whereas ivabradine only accounted for ~4% of the subjects. Ivabradine as a treatment group only appeared in the trial by Villano et al,[16] and the results showed that 1 of the 5 SAQ scores were improved with ivabradine treatment.

There are a number of limitations to the present analysis. First, the design of the included studies differed in several substantive ways, ranging from the populations enrolled to the detection of coronary microvascular function and to the type and

administration of the intervention drugs. Although these characteristics may account for the varying results of the individual studies, they do not significantly detract from the primary objective of the RCTs, which is to assess the effects of antianginal drugs on coronary microvascular function. Second, this meta-analysis lacks data from Africa and South America, and the results may therefore not be generalizable to these parts of the world. Additional data regarding the efficacy of antianginal drugs for CMD are necessary in these continents, and these data from Europe, Asia, and North America also need to be expanded. In addition, statistically significant differences were found in the meaningful secondary end points. Because of the small number of included studies, meta-regression analysis is limited. However, from a clinical point of view, it is possible that BMI, CMD, and the duration of the drug intervention are the sources of heterogeneity. Lastly, the mean follow-up time for the duration of the medication intervention was 3.3 weeks. More extended follow-up would have been highly desirable, and it is possible that the long-term persistence of CMD is associated with the occurrence of MACE.

CONCLUSIONS

The results of the present meta-analysis show that ranolazine improves the global MPRI in patients with definite CMD and the mid-subendocardial MPRI with suspicious CMD, and nicorandil reduces the IMR. In addition, ranolazine and ivabradine reduce angina. Notably, in this meta-analysis, nicorandil was given either intravenously or intracoronary, whereas ranolazine and ivabradine were given orally. Thus, the former reflects an acute protective effect of microcirculation, and the latter two reflect a chronic effect. It is not clear how effective the combination of drugs is at present. Moreover, it is possible that the IMR and mid-subendocardial MPRI are more sensitive than the CFR and global MPRI in evaluating coronary microvascular function. Large clinical trials and trials on different continents need to be conducted to further determine the effects of antianginal drugs in the treatment of coronary microvascular function.

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Drs. Huang and Chen designed the study; Drs. Zhu and Xu performed the study; Drs. Zhu, Xu, and Zhao analyzed the data; Drs. Zhu, Xu, and Zheng wrote the paper; and Drs. Huang, Fang, and Chen revised the paper.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article. Study sponsors are not involved in anything related to this article.

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diagnose significant coronary artery disease and predict cardiac events. *Circ J*. 2015;79:15–23.
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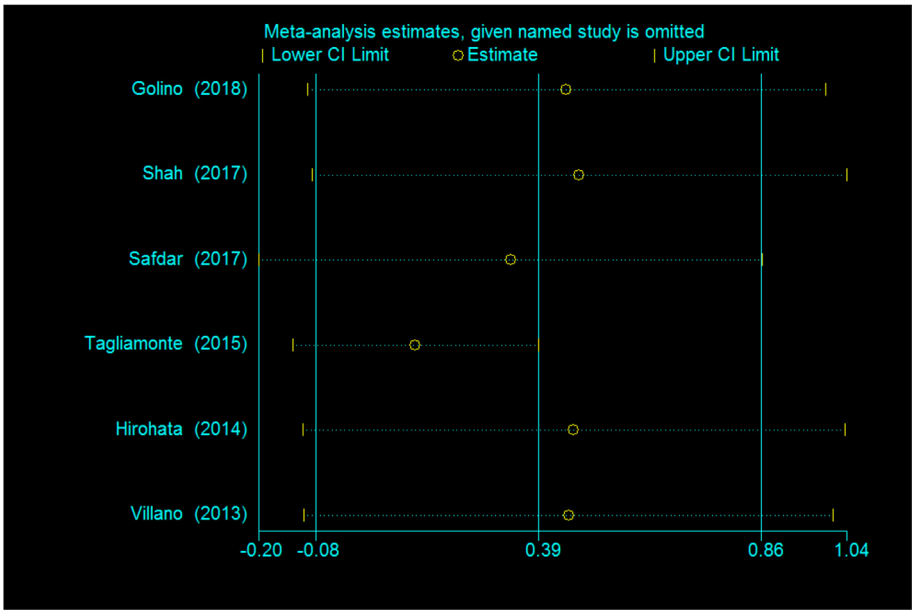
APPENDIX

A. SUPPLEMENTARY DATA

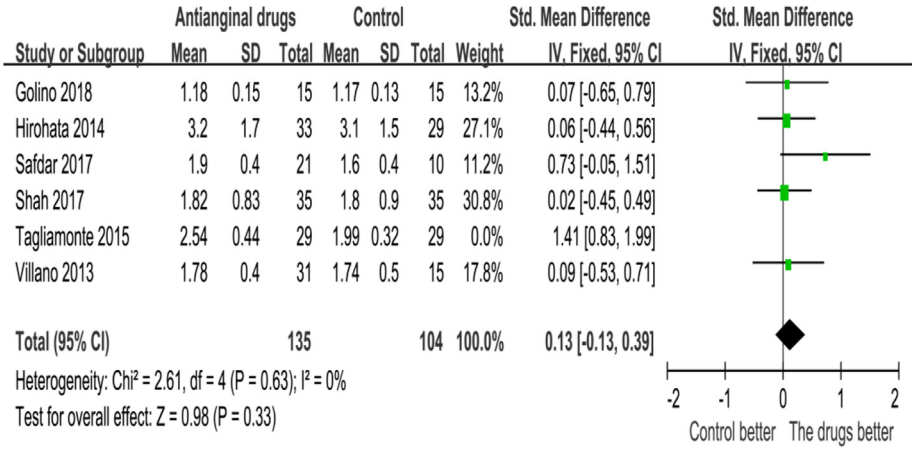
The following is the Supplementary data to this article:

a

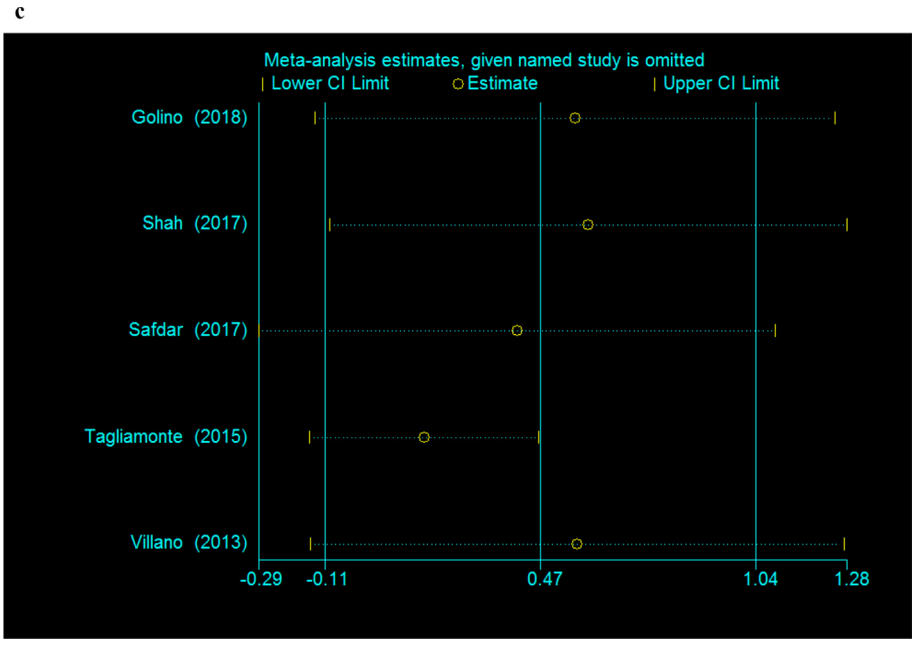


Supplementary Fig. 1a. Sensitivity analysis of CFR. CFR: coronary flow reserve.

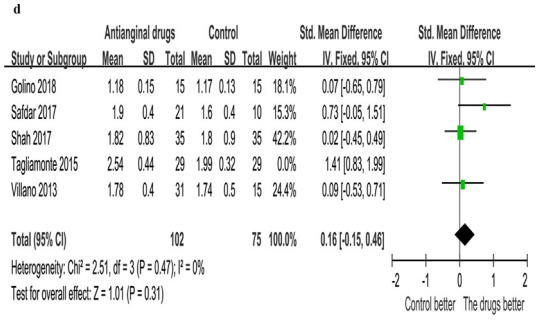
b



Supplementary Fig. 1b. After this outlier study removed, forest plot showing effects of the new antianginal drugs (ranolazine, ivabradine and nicorandil) on change of CFR. CFR: coronary flow reserve.

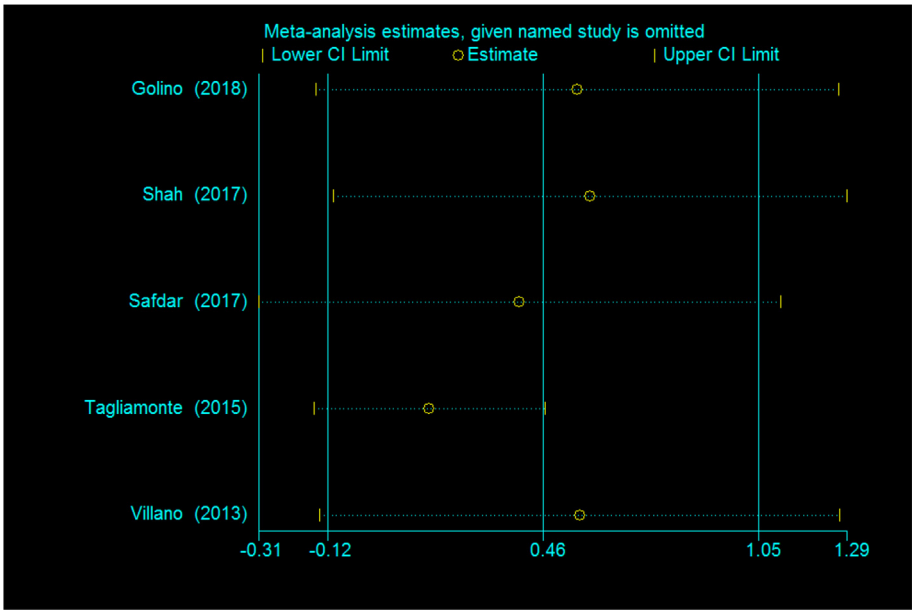


Supplementary Fig. 1c. Sensitivity analysis of CFR in the baseline CFR < 2.5 subgroup. CFR: coronary flow reserve.



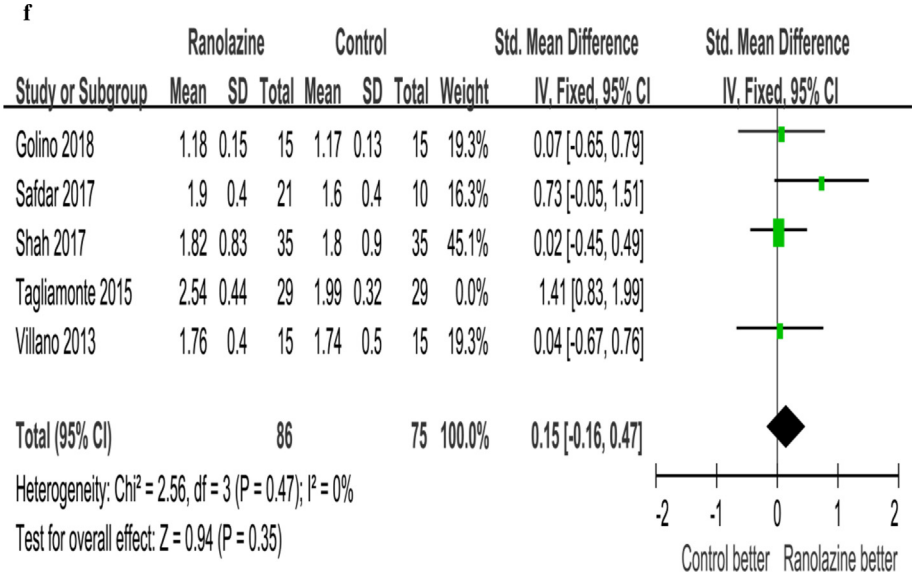
Supplementary Fig. 1d. After this outlier study removed, forest plot showing effects of the new antianginal drugs (ranolazine, ivabradine and nicorandil) on change of CFR in the baseline CFR < 2.5 subgroup. CFR: coronary flow reserve.

e



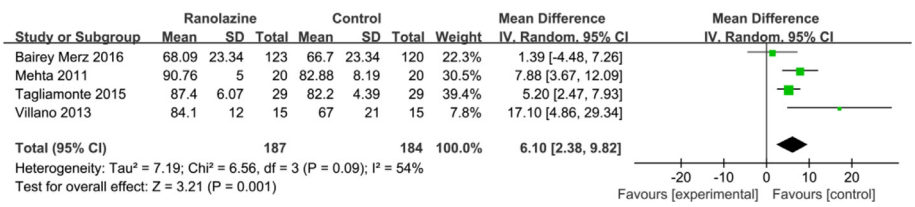
Supplementary Fig. 1e. Sensitivity analysis of CFR in the ranolazine group. CFR: coronary flow reserve.

f



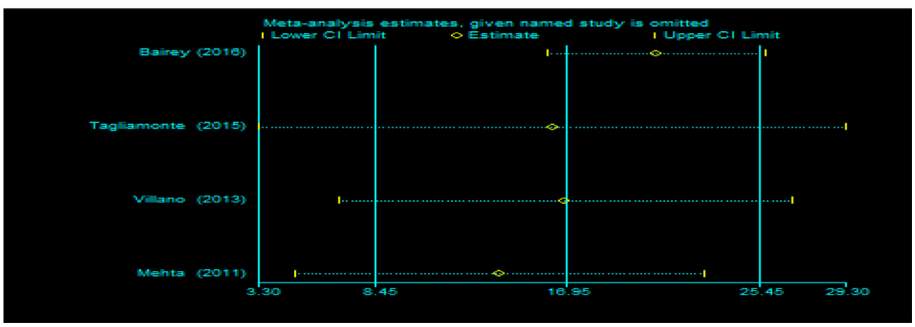
Supplementary Fig. 1f. After this outlier study removed, forest plot showing effects of ranolazine on change of CFR in the baseline CFR < 2.5 subgroup. CFR: coronary flow reserve.

a



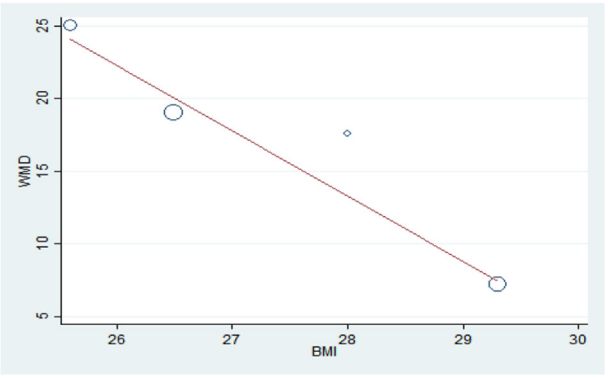
Supplementary Fig. 2a. Forest plot showing the effects of ranolazine on SAQ physical limitations.

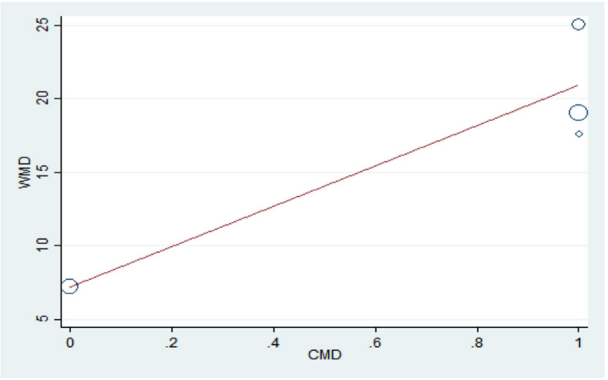
b



Supplementary Fig. 2b. Sensitivity analysis of SAQ angina stability. SAQ: Seattle Angina Questionnaire.

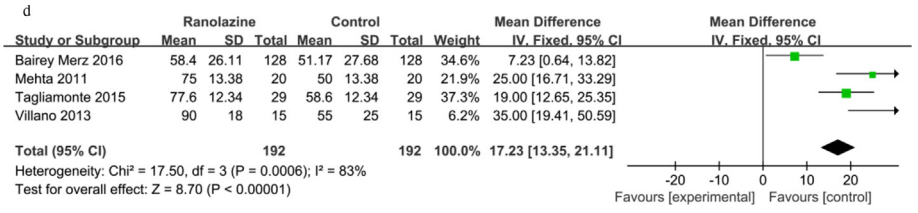
c





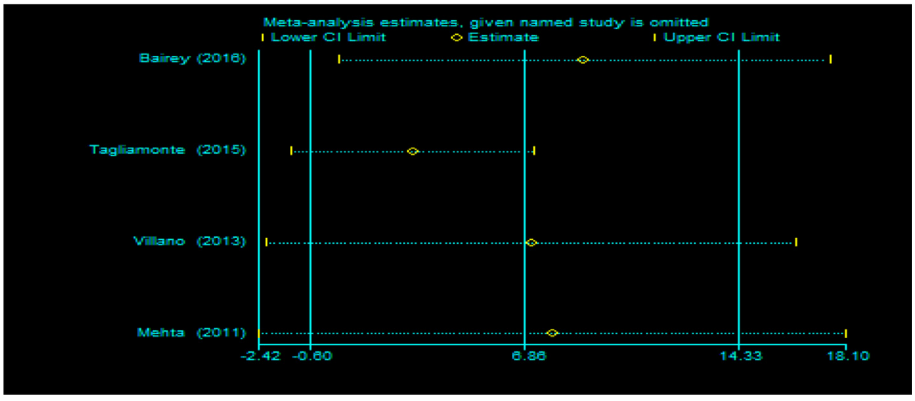
Supplementary Fig. 2c. Meta-regression revealing the relationship between covariate (BMI) and SAQ angina stability. BMI: body mass index.(τ^2=0, I^2=0%, R^2=100%, P=0.075). Meta-regression revealing the relationship between covariate (definite CMD) and SAQ angina stability. CMD: coronary microvascular dysfunction.(τ^2=0, I^2=0%, R^2=100%, P=0.082).

d



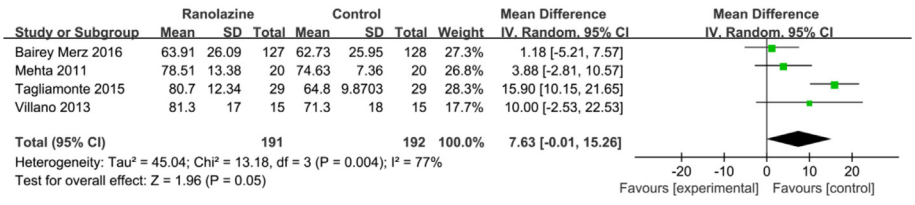
Supplementary Fig. 2d. Forest plot showing the effects of ranolazine on SAQ angina stability.

e



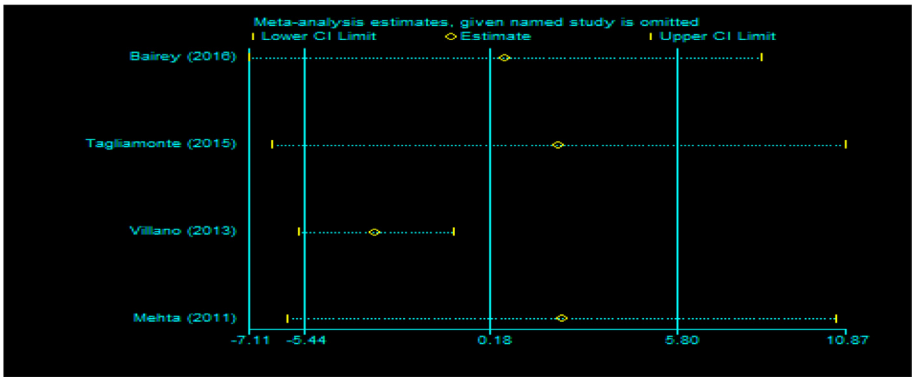
Supplementary Fig. 2e. Sensitivity analysis of SAQ angina frequency. SAQ: Seattle Angina Questionnaire.

f



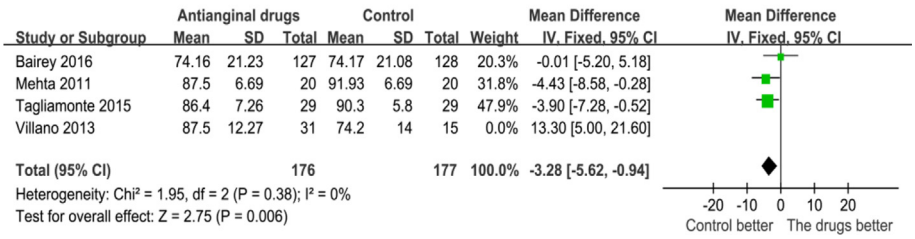
Supplementary Fig. 2f. Forest plot showing the effects of ranolazine on SAQ angina frequency.

g



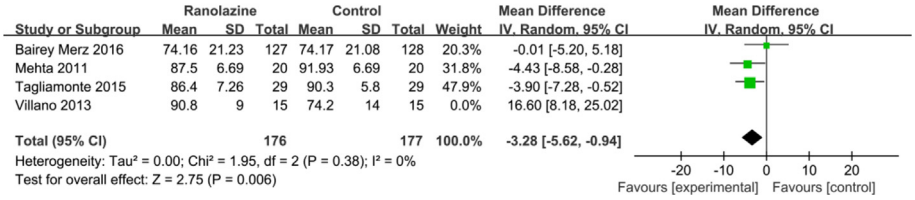
Supplementary Fig. 2g. Sensitivity analysis of SAQ treatment satisfaction. SAQ: Seattle Angina Questionnaire.

h



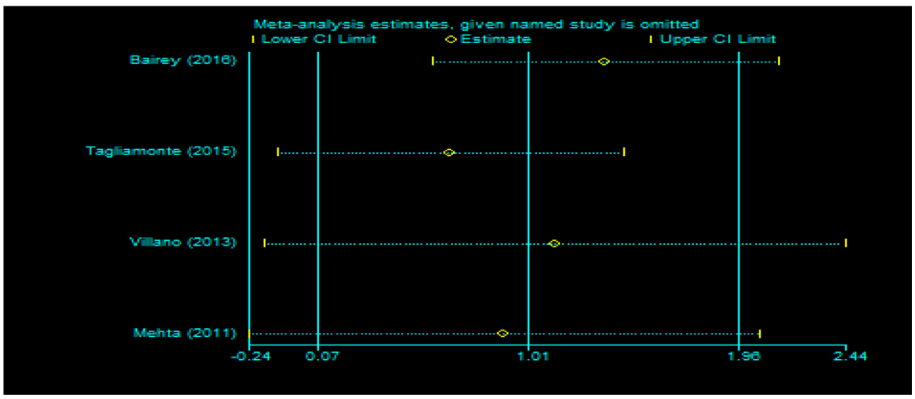
Supplementary Fig. 2h. After this outlier study removed, forest plot showing effects of the new antianginal drugs (ranolazine and ivabradine) on change of SAQ treatment satisfaction. SAQ: Seattle Angina Questionnaire.

i

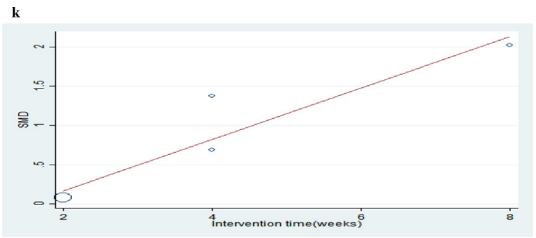


Supplementary Fig. 2i. Forest plot showing the effects of ranolazine on the treatment satisfaction.

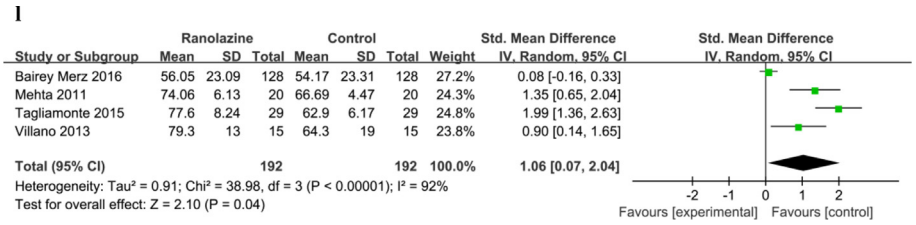
j



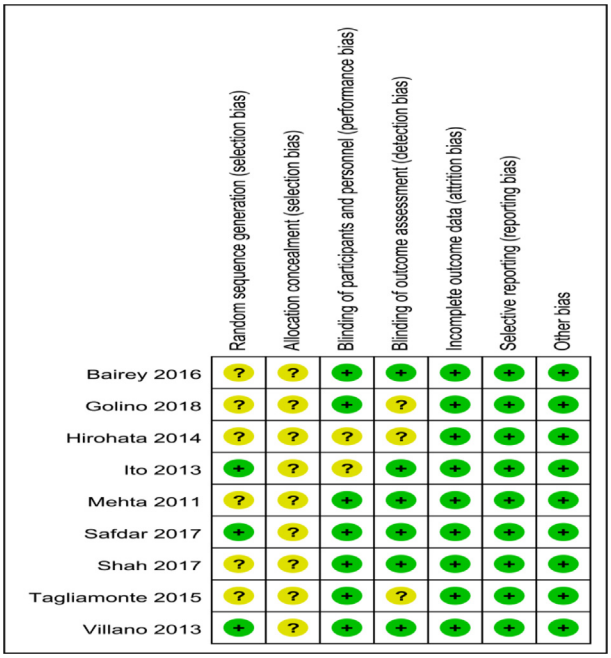
Supplementary Fig. 2j. Sensitivity analysis of QoL. QoL: quality of life.



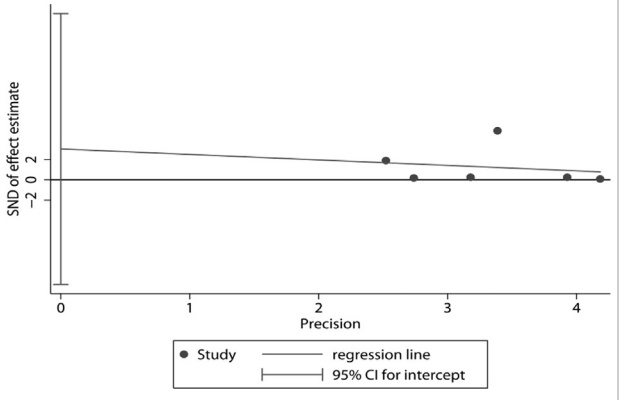
Supplementary Fig. 2k. Meta-regression revealing the relationship between covariate (the duration of intervention drugs) and QoL. QoL: quality of life. (τ^2=0.04, I^2=34.62%, R^2=94.27%, P=0.05).



Supplementary Fig. 2l. Forest plot showing the effects of ranolazine on the QoL score.



Supplementary Fig. 3. Risk of bias summary.



Supplementary Fig. 4. Egger's funnel plot for evaluating the publication bias in the studys of CFR. CFR: coronary flow reserve.

Supplementary Table 1. Main characteristics of trials included in the meta-analysis. ADO: adenosine; CPT: cold pressor test; ISMN: isosorbide-5-mononitrate; PTCA: percutaneous transluminal coronary angioplasty; CFR: coronary flow reserve; CMRI: cardiac magnetic resonance imaging; MPRI: myocardial perfusion reserve index; CMD: coronary microvascular dysfunction; CAD: coronary artery disease; SPECT: single photon emission tomography; ACH: acetylcholine; WISE: Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE); WHO: World Health Organization; MI: myocardial infarction; BP: blood pressure; CrCl: creatinine clearance; PFR: peak filling rate; tPFR: time to PFR; SAQ: Seattle Angina Questionnaire; QoL: quality of life; PET-CT: positron emission tomography-computed tomography; CT: computed tomography; PET: positron emission tomography; ED: emergency department; ECG: electrocardiograph; IMR: index of microvascular resistance; PCI: percutaneous coronary intervention; Cr: creatinine; IVUS: intravascular ultrasound; MVA: microvascular angina; CBF: coronary blood flow; cTFC: corrected TIMI frame count.

Characteristics	Golino et al. 2018[24]	Shah et al. 2017[9]	Safdar et al. 2017[25]	Bairey Merz et al. 2016[15]	Tagliamonte et al. 2015[27]	Hirohata et al. 2014[11]	Villano et al. 2013[16]	Ito et al. 2013[26]	Mehta, et al. 2011[10]
Design	Prospective, randomized, controlled, crossover, single-blind	Prospective, randomized, controlled, crossover, double-blind	Prospective, randomized, controlled, parallel, double-blind	Prospective, randomized, controlled, crossover, double-blind	Prospective, randomized, controlled, parallel, double-blind	Prospective, randomized, controlled, parallel, non-blind	Prospective, randomized, controlled, parallel, double-blind	Prospective, randomized, controlled, crossover, uncertain-blind	Prospective, randomized, controlled, crossover, double-blind
Coronary microvascular function test	Assessment of coronary microvascular dilator response to ADO and CPT by transthoracic echo-color-Doppler. Baseline CFR-ADO: 1.33 ± 0.16 < 2.5; CFR-CPT: 1.15 ± 0.09 < 2.5	CFR was measured by PET-CT. Baseline CFR: 1.76 ± 0.49 < 2.5	CFR was measured by PET-CT. Baseline CFR: 1.76 ± 0.49 < 2.5	MPRI was obtained by CMRI, and CFR was measured by Doppler flow-wire following intracoronary adenosine injections. Baseline global MPRI: 1.6 ± 0.3 < 2 (n = 67); Baseline CFR: 2.2 ± 0.2 < 2.5 (n = 35)	CFR was measured by Doppler ultrasound system. Baseline CFR: 1.93 ± 0.30 < 2.5	CFR and IMR were measured by thermodilution techniques. Baseline IMR: 14.82 ± 9.34; Baseline CFR: 1.75 ± 0.66 < 2.5 (The accuracy of CFR in evaluating CMD was impaired because the baseline time was measured before the relief of epicardial stenosis.)	Assessment of coronary microvascular dilator response to ADO and CPT by transthoracic echo-color-Doppler. Baseline CFR-ADO: 1.99 ± 0.81 < 2.5; CFR-CPT: 1.71 ± 0.40< 2.5	IMR was measured by thermodilution techniques. Baseline IMR: 28.58 ± 17.06	MPRI was obtained by CMRI, and CFR was measured by Doppler flow-wire following intracoronary adenosine injections. Baseline global MPRI: 1.5 ± 0.56 < 2
Administration method	Patients received 3 weeks each, either ISMN (20 mg twice a day in a slow-release formulation) or ranolazine (375 mg twice a day).	Patients received ranolazine or placebo 500 mg twice a day in 1 week and ranolazine or placebo 1000 mg twice a day in 3 weeks.	Patients received ranolazine or placebo 500 mg twice a day in 1 week and ranolazine or placebo 1000 mg twice a day in 3 weeks.	Patients received ranolazine or placebo 500 mg twice a day in first week and ranolazine or placebo 1000 mg twice a day in Second week.	Patients received ranolazine or placebo 350 mg twice a day in 4 weeks and ranolazine or placebo 500 mg twice a day in an additional 4 weeks.	Nicorandil was intravenously administered as a 6 mg bolus injection just before PCI and as a constant infusion at 6 mg/h for 24 h (total 150 mg) thereafter.	Patients received 1 of the following drug regimens for a period of 4 weeks: (1) ivabradine, 5 mg twice daily, (2) ranolazine, 375 mg twice daily, or (3) placebo twice daily.	Of the total 60 patients, 30 patients were first administered nitroglycerin via an intracoronary injection of 250 μg, and the other 30 patients were first given 2 mg intracoronary nicorandil in the same manner.	Patients received ranolazine or placebo 500 mg twice a day in 2 weeks and ranolazine or placebo 1000 mg twice a day in an additional 2 weeks.
Washout period	One week	Three days	–	Two weeks	–	–	–	None	Two weeks
Dropouts	None	3	6	14	None	None	None	None	None
Main inclusion criteria	1. Previous PTCA with stenting; 2. exercise-induced ST-segment depression ≥1 mm, with or without a history of typical effort angina; 3. no bstructive coronary artery disease at a recent (<6 months) coronary angiography.	1. Patients with diabetes mellitus; 2. stable angina and/or exertional dyspnea; 3. exercise tolerance of at least 3 metabolic equivalents on a treadmill or bicycle exercise tolerance test.	1. Adults aged 30 years and older; 2. chest pain within 24 h of ED presentation; 3. reduced CFR (CFR<2 corrected for rate pressure product or <2.5 uncorrected).	1. Men or women age >18 yrs from diverse racial/ethnic groups; 2. competent to give informed consent; 3. patients with chronic angina or its equivalent; 4. coronary angiogram revealing CMD with no obstructive CAD (epicardial coronary stenosis <50% luminal diameter stenosis); or measured noninvasively using the Society of Cardiovascular Computed Tomography threshold of <50% stenosis. 5. left ventricular ejection fraction ≥45%; 6. objective evidence of ischemia by	1. Symptomatic for angina pectoris; 2. previously performed Tc-99m MIBI myocardial perfusion imaging, to confirm myocardial ischemia, with scans acquired before and after exercise on a treadmill, under a standard Bruce protocol; 3. coronary angiography was performed using standard technique. Coronary stenosis was evaluated using multiple projections and quantitative analysis of the % diameter stenosis was then performed. Obstructive coronary disease was excluded if percentage of stenosis was <70%.	1. Patients with clinically stable angina pectoris scheduled for elective PCI; 2. using conventional technique, of the left anterior descending coronary artery.	1. A diagnosis of stable primary MVA based on the presence of (i) a history of typical effort angina, (ii) exercise-induced ST-segment depression ≥ 1 mm, (iii) normal coronary angiography, (iv) absence of any specific cardiac disease including vasospastic angina, (v) normal echocardiographic examination including absence of left ventricular hypertrophy, and (vi) a CFR < 2.5 in the left anterior descending coronary artery as assessed by CBF response to adenosine at transthoracic	1. Age >18 years; 2. for their first episode of STEMI within 24 h of the onset of symptoms.	1. Women with signs and symptoms of myocardial ischemia (chest pain and abnormal routine stress testing); 2. no obstructive CAD (<50% epicardial coronary stenosis in all epicardial coronary arteries) on clinically indicated coronary angiography, who had an abnormal adenosine stress CMR (≥10% ischemic myocardium) within the previous 12 months. 3. no

(*continued on next page*)

Supplementary Table 1. (*Continued*)

Characteristics	Golino et al. 2018[24]	Shah et al. 2017[9]	Safdar et al. 2017[25]	Bairey Merz et al. 2016[15]	Tagliamonte et al. 2015[27]	Hirohata et al. 2014[11]	Villano et al. 2013[16]	Ito et al. 2013[26]	Mehta, et al. 2011[10]
				noninvasive methods such as exercise stress test, stress Echo, CMRI or SPECT; 7. patients with CMD defined as an invasive measured CFR <2.5 or ACH response of no dilation or constriction, determined by local site read, or a CMRI derived MPRI ≤2.0. 8. patients must have withdrawn from ranolazine at least 2 weeks prior to study entry. 9. either a qualifying WISE or clinical CMRI scan must be completed within 2.5-yrs ±1 month of study participation. 10. qualifying angiograms must have been within 2.5 yrs ±1 month of study enrollment.			Doppler echocardiography; 2. suboptimal control of symptoms on conventional anti-ischemic therapy, as indicated by the occurrence of ≥ 1 episode per week of angina.		intercurrent cardiac events occurred between the qualifying CMR scan and trial enrollment and completion.
Main exclusion criteria	1. Signifcant systemic disease (e.g., liver and/or kidney failure, tumors, neuromuscular disorders, psychiatric diseases); 2. ECG abnormalities that could interfere with the assessment of ST-segment during exercise; 3. previous consumption of the drugs under investigation and no contraindications to their administration	1. Patients with obstructive CAD (defined as ≥50% luminal stenosis) on clinically indicated invasive coronary angiography or coronary CT angiography within 1 year prior to study screening; 2. A history of cardiomyopathy (left ventricular ejection fraction <40%); 3. moderate-severe valvular heart disease; 4. uncontrolled hypertension (systolic blood pressure >180 mm Hg); 5. renal impairment (estimated glomerular filtration rate <50 mL/min per 1.73 m2); 6. a contraindication to ranolazine; 7. patients already taking ranolazine for clinical indications.	1. Coronary artery calcification; 2. acute coronary syndrome; 3. hypertensive crisis (blood pressure >180/110 mmHg); 4. known CAD; 5. left ventricular ejection fraction <35%; 6. dialysis; 7. liver cirrhosis; 8. aortic stenosis; 9. active substance abuse; 10. current use of potent CYP3A4-inhibitors; 11. inducers or QTc-prolonging drugs, baseline ECG QTc >580 ms; 12. pregnancy; 13. Inability to consent or communicate in English.	1. Acute coronary syndrome (defined by WHO), cardiogenic shock or requiring inotropic or intra-aortic balloon support; 2. planned percutaneous coronary intervention or coronary bypass surgery or established obstructive CAD with ischemia eligible for revascularization, acute MI; 3. prior non-cardiac illness with estimated life expectancy <4-yrs; 4. unable to give informed consent; 5. allergy or contra-indication to CMRI testing, including renal failure, claustrophobia, and asthma, uncontrolled moderate hypertension (sitting BP > 160/95 mmHg with measurements recorded on at least 2 occasions), other conditions likely to influence outcomes: Severe lung, creatinine >1.8 or CrCl ≤50 ml/min) or hepatic disease; 6. surgically uncorrected significant congenital or valvular heart disease and other disease likely to be fatal or require frequent	1. Hepatic insufficiency; 2.1. prolonged QT; 3. renal failure; 4. use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides, and HIV protease inhibitors; 5. life expectancy <6 months; 6. atrial fibrillation; 7. left bundle branch block on ECG; 8. primary valvular heart disease; 9. hypertrophic cardiomyopathy; 10. previous acute coronary syndrome; 11. left ventricular systolic dysfunction with ejection fraction less than 55%.	Patients with complicated lesions, such as excessive tortuosity or calcified lesions; 2. unable to cross with pressure wire or IVUS; 3. chronic renal failure (Cr.>1.5); 4. unstable patients; 5. recent myocardial infarction within four weeks; 6. poor ejection fraction <25%.	1. Previous consumption of the drugs under investigation; 2. apparent contraindications to ivabradine and ranolazine administration.	1. The presence of cardiac shock; 2. severe hepatic and/or renal dysfunction; 3. severe hypovolemia; 4. a history of myocardial infarction or drug allergy.	1. contraindications to withholding nitrates, calcium channel agents, and alpha and beta-adrenergic blockers for 24 h before testing; 2. contraindications to CMR including implantable cardioverter-defibrillators, pacemakers, and severe claustrophobia; 3. hepatic insufficiency, prolonged QT, renal failure; 4. use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides, and HIV protease inhibitors; 5. women younger than 18 years of age (3 women of child-bearing age were enrolled), pregnant, or breastfeeding; 6. women taking drugs that prolong the QT interval; 7. life expectancy <6 months.

Supplementary Table 1. (*Continued*)

Characteristics	Golino et al. 2018[24]	Shah et al. 2017[9]	Safdar et al. 2017[25]	Bairey Merz et al. 2016[15]	Tagliamonte et al. 2015[27]	Hirohata et al. 2014[11]	Villano et al. 2013[16]	Ito et al. 2013[26]	Mehta, et al. 2011[10]
				hospitalization within the next six months; 7. adherence or retention reasons; 8. unwilling to complete follow-up evaluation including repeat testing, documented obstructive hypertrophic cardiomyopathy; 9. aortic stenosis (valve area <1.5 cm); 10. LV dysfunction (ejection fraction <45%); 11. history of significant cocaine or amphetamine abuse; 12. taking potent CYP3A4 inhibitors (ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir); 13. women who are pregnant.					
Primary endpoint	CFR and diastolic left ventricular	CFR and left ventricular myocardial blood flow	CFR	MPRI, left ventricular PFR and tPFR	CFR and left ventricular ejection fraction	CFR, IMR and FFR	SAQ and EuroQoL	IMR	MPRI
Secondary endpoints	Exercise stress test	Hemodynamic parameters at rest and during exercise, diastolic function, and serum biomarkers	Adverse events	SAQ, SAQ-7, functional capacity/status, and QoL	SAQ	CK-MB, troponin I and IVUS parameters	CFR and exercise stress test	cTFC, CK and CK-MB	SAQ and QoL
Location	Italy	United States	United States	United States	Italy	Japan	Italy	Japan	United States

Supplementary Table 2. Main characteristics of patients enrolled among trials included in the meta-analysis. ISMN: isosorbide-5-mononitrate, NTG: nitroglycerine, PCI: percutaneous coronary intervention, NR:Not Report, BMI: body mass index, CAD: coronary artery disease.

Characteristics	Golino et al. 2018[24]	Shah et al. 2017[9]	Safdar et al. 2017[25]	Bairey Merz et al. 2016[15]	Tagliamonte et al. 2015[27]	Hirohata et al. 2014[11]	Villano et al. 2013[16]	Ito et al. 2013[26]	Mehta, et al. 2011[10]
n in the treatment arm	15	35	21	128	29	29	31	30	20
n in the control arm	15	35	10	125	29	33	15	30	20
Intervention drug	Ranolazine	Ranolazine	Ranolazine	Ranolazine	Ranolazine	Nicorandil	Ranolazine, Ivabradine	Nicorandil	Ranolazine
Control drug	ISMN	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	NTG	Placebo
Age	67.3 ± 5.4	64.0 ± 4.6	50.0 ± 5.7	55.2 ± 9.8	65.5 ± 10.5	70.7 ± 11.6	58 ± 10.9	65.1 ± 13.1	57.0 ± 11.0
Female, %	6.7	49.0	71.0	96.0	32.8	27.4	80.4	11.7	100
Hypertension, %	80.0	86.0	61.3	53.9	63.8	63.3	76.1	53.3	50.0
Diabetics, %	47.0	100	29.0	18.0	22.4	22.6	NR	41.7	NR
Hyperlipidemia, %	100	94.0	29.0	54.7	51.7	48.7	63.0	55.0	60.0
Smoking, current/all, %	NR/NR	6.0/NR	NR/54.8	1.7/31.3	NR/33.3	NR/61.7	13.0/NR	NR/78.3	0/50.0
BMI	26.3 ± 2.9	31.4 ±7.0	41.1 ± 10.4	29.3 ± 7.6	26.5 ± 4.8	NR	28.0 ± 4.5	NR	25.6 ± 3.8
Family history of CAD, %	53.0	31.0	38.7	64.8	24.1	NR	78.2	NR	70.0
PCI after admission	No	No	No	No	No	Yes	No	Yes	No